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(54) Title: ARYL UREA DERIVATIVES

(57) Abstract: A method of treating a condition associated with the CB-1 receptor, in particular obesity, by administering an effective amount of an aryl urea CB-1 receptor modulating compound to a subject in need of such treatment.

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ARYL UREA DERIVATIVES

BACKGROUND OF THE INVENTION

The present invention is directed to aryl urea derivatives. In particular, the present invention is directed to aryl urea derivatives useful in the treatment of conditions associated with the cannabinoid 1 receptor, in particular obesity.

Obesity, defined as a high ratio of body fat to lean body mass, is understood to be a risk factor for several potentially life-threatening diseases including atherosclerosis, hypertension, type II diabetes, stroke, pulmonary embolism, gallbladder disease, sleep apnea, and colon and postmenopausal breast cancer. Thus, the number of people suffering from such diseases can be lowered if obesity can be minimized without increasing other risk factors.

Presently, obesity treatments include diets to lower the caloric intake, and exercises to increase the caloric outflow. As the continuing onslaught of new diet and exercise regimes show, such programs are often ineffective because many patients have difficulty following such programs long-term. Surgery to physically remove fat or surgery, such as gastric partitioning, jejunoileal bypass, and bagotomy, to reduce stomach capacity, entail considerable risk. Thus, there remains a need for new procedures to treat obesity.

Obesity treatments also include administering drugs. As described in D. Spanswick and K. Lee, *Expert Opinion*, 8(1):217-237(2003), such drugs include appetite suppressants, inhibitors of fat absorption, enhancers of energy expenditure, and stimulators of fat mobilization. Among the various central nervous system (CNS) sites susceptible as therapeutic targets for anti-obesity drugs is the cannabinoid 1 (CB1, CB-1 or CB_1) receptor. Inhibition of the CB-1 receptor by, for example, administering a CB-1 antagonist acts to suppress appetite. Further, inhibition of CB-1 is useful for the prophylactic use to prevent overweight, to assist in regulating food intake, and to assist as a diet aid. Compounds that target the CB-1 receptor include SR-141716, a selective CB-1 receptor antagonist (see *ibid.* at 230). Nevertheless, it would be desirable to develop other compounds that inhibit CB-1 for the treatment of obesity.

As described above, inhibition of the CB-1 receptor is useful to suppress appetite, to prophylactically prevent overweight, to assist in regulating food intake, to assist as a diet aid, and to treat obesity. Such inhibition includes modulating the CB-1 receptor by applying an antagonist or by applying an inverse agonist. Thus, there is a need for novel compounds and novel administration of CB-1 modulators, e.g. antagonist or inverse agonist compounds, to suppress appetite, to prophylactically prevent overweight, to assist in regulating food intake, to assist as a diet aid, and to treat obesity.

As the CB-1 receptor seems to be involved in the brain's reward system, CB-1 modulator compounds may also find use in the treatment of addictive disorders such as tobacco smoking, heroin addiction (see Solinas M et al, *J. Pharmacol. Exp. Ther.*, 2003 Jul;306(1):93-102); relapse to cocaine-seeking (see De Vries TJ et al, *Nat. Med.*, 2001 Oct;7(10):1151-4); and alcoholism (see Hungund BL et al, *J. Neurochem.*, 2003 Feb;84(4):698-704). CB-1 is also involved in other central functions besides the rewards system. CB-1 receptor activation by cannabis or other CB-1 agonists leads to memory

impairment. CB-1 antagonists are therefore good candidate agents for memory enhancement (see Reibaud M et al, *Eur. J. Pharmacol.*, 1999 Aug 20;379(1):R1-2, and Terranova JP et al, *Psychopharmacology (Berl).*, 1996 Jul;126(2):165-72). CB-1 activation can also lead to impairment in movement and movement disorders like Parkinson's disease have been associated with elevated brain endocannabinoids. CB-1 antagonism would therefore be a good candidate treatment for Parkinson's disease (see Di Marzo V et al, *FASEB J.*, 2000 Jul;14(10):1432-8).

Central CB-1 receptor signaling is functionally linked to monoaminergic neurotransmission. This makes CB-1 antagonists candidates for the treatment of psychosis, affective and cognitive disorders brought about by disturbances in any of the central monoaminergic systems.

In addition to its strong central expression, CB-1 is expressed in some peripheral tissues. CB-1 receptors expressed on nerve endings in the gastrointestinal tract depress gastrointestinal motility, mainly by inhibiting ongoing contractile transmitter release. Antagonists of CB-1 receptor could thus find use in pathological states consisting of decreased intestinal motility such as Paralytic ileus caused by peritonitis, surgery, or other noxious situations (see Mascolo N et al, *FASEB J.*, 2002 Dec;16(14):1973-5).

CB-1 receptors also play a role in vascular endothelial cells where they mediate the hypotensive effects of platelet and macrophage-derived endocannabinoids. CB-1 antagonists would be useful agents in inhibiting endotoxin-induced or cirrhotic hypotension (see Batkai S et al, *Nat Med.*, 2001 Jul;7(7):827-32) both of which are characterized by elevated levels of endocannabinoids.

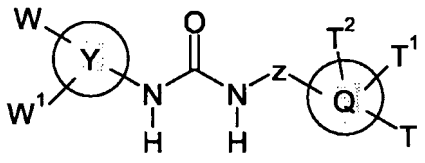
Various aryl urea derivatives are known, however the use of such compounds as CB-1 receptor modulators has not previously been described or suggested.

SUMMARY OF THE INVENTION

A method of treating a condition, e.g. obesity, associated with the CB-1 receptor, by administering an effective amount of an aryl urea CB-1 receptor modulator compound to a subject in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of treating a condition associated with the CB-1 receptor by administering to a subject in need of such treatment a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

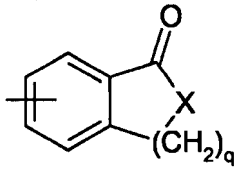
Y is phenyl, a 5- or 6-membered heteroaryl group, or a 9-membered bicyclic heteroaryl group attached to the urea through the 5-membered ring;

W is $COOR^1$, COR^1, C_{1-6}alkyl, C_{1-3}fluoroalkyl, C_{1-6}alkoxy, phenoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkoxy, C_{1-6}alkylthio, C_{3-6}cycloalkyl, chloro, fluoro, nitrile, $-(CH_2)_m-NR^2R^3$, $-O(CH_2)_n-NR^2R^3$, or 5- or 6-membered heteroaryl optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, C_{1-3}fluoroalkyl, C_{1-3}alkoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkyl, chloro, fluoro and $-(CH_2)_m-NR^2R^3$; or when Y is a 9-membered bicyclic heteroaryl group attached to the urea through the 5-membered ring, or when Z is C_{1-3}alkylene or C_{2-3}alkenylene, then W may be hydrogen;

W^1 is hydrogen, halogen, C_{1-3}alkyl, hydroxy or C_{1-3}alkoxy;

or W and W^1, when attached to adjacent carbon atoms on Y, together form a group $-O-(CH_2)_p-O-$, wherein p is 1, 2 or 3;

or the group formed from -Y, -(W) and $-(W^1)$ is:



wherein X is O or CH_2 and q is 1 or 2;

Z is C_{1-3}alkylene, C_{2-3}alkenylene or a bond;

Q is phenyl, or a 5- to 10-membered mono- or bicyclic heteroaryl group;

T is hydrogen, halogen, nitro, nitrile, $COOR^1$, COR^1, $-(CH_2)_m-NR^2R^3$, $CONHCH_2COOH$, C_{1-6}alkyl optionally substituted by $COOR^4$ or OR^4, C_{1-3}fluoroalkyl, C_{1-6}alkoxy, C_{1-3}fluoroalkoxy, C_{1-6}alkylthio, SOR^5, SO_2R^5; or a C_{3-6}cycloalkyl group, 5- to 7-membered heterocyclyl group or 5- to 10-membered heteroaryl group any one of which is optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, C_{1-3}fluoroalkyl, C_{1-3}alkoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkyl, chloro, fluoro, hydroxy and $-(CH_2)_m-NR^2R^3$;

T^1 and T^2 are independently selected from hydrogen, halogen, hydroxy, C_{1-3}alkyl and C_{1-3}alkoxy;

or T and T^1, when attached to adjacent carbon atoms on Q, together form a group $-O-(CH_2)_p-O-$, wherein p is 1, 2 or 3;

m is 0, 1, 2 or 3;

n is 2 or 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or a 5- or 6-membered heteroaryl or heterocyclyl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl and C_{3-6}cycloalkyl, or R^2 and R^3 together with the nitrogen to which they are attached form a 5- to 7-membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and NR^4, and optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy;

R^4 is hydrogen or C_{1-3}alkyl; and

R^5 is C_{1-6}alkyl or C_{3-6}cycloalkyl.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the treatment of a condition associated with the CB-1 receptor.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition associated with the CB-1 receptor.

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600.

Particular examples of 5- or 6-membered heteroaryl groups that Y may represent include thienyl, thiazolyl and thiadiazolyl.

Particular examples of 9-membered bicyclic heteroaryl groups that Y may represent include benzothienyl and benzothiazolyl, especially benzothien-2-yl and benzothiazol-2-yl.

A specific group of compounds of formula (I) which may be mentioned are those where Y is phenyl.

When Y is phenyl, W is preferably $COOR^1$ especially COOEt, or COR^1, C_{1-6}alkoxy, C_{1-6}alkylthio, fluoro, chloro, C_{1-3}alkoxyC_{1-3}alkoxy, $-(CH_2)_m-NR^2R^3$, $-O(CH_2)_n-NR^2R^3$, or 5- or 6-membered heteroaryl optionally substituted by C_{1-3}alkyl. Particular W groups which may be mentioned are chloro, C_{1-3}alkoxyC_{1-3}alkoxy, $-(CH_2)_m-NR^2R^3$ and $-O(CH_2)_n-NR^2R^3$ where $-NR^2R^3$, is preferably morpholinyl.

Heteroaryl groups which W may represent include 5- or 6-membered heteroaryl groups containing 1 or 2 nitrogen atoms such as pyrazole, pyrrole, imidazole, pyrimidine or pyridine.

W^1 is preferably hydrogen, halogen or C_{1-3}alkoxy, more preferably hydrogen.

Z is preferably C_2alkylene, C_2alkenylene or a bond, more preferably C_2alkylene or a bond, especially a bond.

Q is preferably phenyl, pyridyl or a 9-membered bicyclic heteroaryl group such as benzothienyl, benzothiazolyl, or indazole, especially benzothien-2-yl, benzothiazol-2-yl, or indazol-5-yl.

Q is more preferably phenyl, or a 9-membered bicyclic heteroaryl group such as benzothienyl or benzothiazolyl, especially benzothien-2-yl or benzothiazol-2-yl.

A specific group of compounds of formula (I) which may be mentioned are those where Q is phenyl or pyridyl, especially phenyl.

A group of compounds which may be mentioned are those where T is hydrogen, halogen, nitro, nitrile, $COOR^1$, COR^1, $-(CH_2)_m-NR^2R^3$, $CONHCH_2COOH$, C_{1-6}alkyl optionally substituted by $COOR^4$ or OR^4, C_{1-3}fluoroalkyl, C_{1-6}alkoxy, C_{1-3}fluoroalkoxy, C_{1-6}alkylthio, SOR^5, SO_2R^5; or a C_{3-6}cycloalkyl group, or a 5- or 6-membered heterocyclyl or heteroaryl group any one of which is optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, C_{1-3}fluoroalkyl, C_{1-3}alkoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkyl, chloro, fluoro and $-(CH_2)_m-NR^2R^3$, wherein m is 0, 1, 2 or 3.

T is preferably halogen, $COOR^1$, COR^1, C_{1-6}alkyl, $-(CH_2)_m-NR^2R^3$ optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy, or a

5- to 10-membered heteroaryl group optionally substituted by C_{1-3}alkyl, e.g. a 5- or 6-membered heteroaryl group containing 1 or 2 nitrogen atoms such as pyrazole, pyrrole, imidazole, pyrimidine or pyridine, or thiazole, thiadiazole, oxazole or 3,4-dihydro-1H-isoquinolin-2-yl.

T^1 and T^2 are preferably hydrogen, halogen or hydroxy, more preferably hydrogen or halogen.

T^2 is preferably hydrogen.

A specific group of compounds which may be mentioned are those where T is $-(CH_2)_m-NR^2R^3$, T^1 is halogen, e.g. fluoro, and T^2 is hydrogen.

When T is $-(CH_2)_m-NR^2R^3$, m is preferably 0 and R^2 and R^3 together with the nitrogen to which they are attached preferably form a 5- to 7-membered heterocyclic ring, e.g. a piperidine ring, optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy, e.g. methyl.

W and T are preferably different.

Preferably at least one of Y and Q is phenyl.

Substituents on the groups Y and Q are preferably in the meta and/or para positions relative to the urea, more preferably the para position.

A group of compounds which may be mentioned are those where R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or a 5- or 6-membered heteroaryl group.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I) is selected from the preferred, more preferred or particularly listed groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred and particularly listed groups. The preferences listed above also apply, where applicable, to the compounds of formula (Ia) below.

Specific compounds which may be used in the method of the invention include:

2-[3-(4-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester

2-[3-(3-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester

2-[3-(4-Ethoxycarbonylphenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester

4-Methyl-2-[3-(4-methylsulfanylphenyl)ureido]thiazole-5-carboxylic acid ethyl ester

4-Methyl-2-[3-phenylureido]thiazole-5-carboxylic acid ethyl ester

1-(4-Acetylphenyl)-3-benzo[b]thiophen-2-ylurea

1-Benzo[b]thiophen-2-yl-3-(4-methanesulfonylphenyl)urea

1-Benzo[b]thiophen-2-yl-3-(2-methylphenyl)urea

1-Benzo[b]thiophen-2-yl-3-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)urea

1-Benzo[b]thiophen-2-yl-3-phenylurea

1-Benzo[b]thiophen-2-yl-3-(2,4-difluorophenyl)urea

1-Benzo[b]thiophen-2-yl-3-(4-fluorophenyl)urea

1-(4-Fluorophenyl)-3-(4-methylthiophen-2-yl)urea

1-Phenyl-3-(2-thiophen-2-ylvinyl)urea

1-(2-Chlorophenyl)-3-(2-thiophen-2-ylvinyl)urea

4-[3-(4-Fluoro-2-methylphenyl)ureido]benzoic acid ethyl ester

4-[3-(2,4,6-Trifluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(2,4-Difluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(3,4-Difluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(2-Chloro-4-fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluoro-3-methylphenyl)ureido]benzoic acid ethyl ester
4-[3-(3-Chloro-4-fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluoro-3-methoxyphenyl)ureido]benzoic acid ethyl ester
4-[3-(3-Fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(2-Fluorophenyl)ureido]benzoic acid ethyl ester
1-(4-Ethoxyphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluorophenyl)ureido]-3-methylbenzoic acid methyl ester
4-[3-(4-Fluorophenyl)ureido]-3-hydroxybenzoic acid methyl ester
1-(3-Ethoxyphenyl)-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(4-methoxyphenyl)urea
1-(4-Cyanophenyl)-3-(4-fluorophenyl)urea
1-(4-Acetylphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluoro-3-nitrophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid methyl ester
1-(4-Chlorophenyl)-3-(4-ethoxyphenyl)urea
1,3-Bis(4-acetylphenyl)urea
1-(4-Acetylphenyl)-3-(3-chlorophenyl)urea
1-(4-Acetylphenyl)-3-(4-chlorophenyl)urea
4-(3-Phenylureido)benzoic acid ethyl ester
1-(2-Thiophen-2-ylethyl)-3-(4-methylphenyl)urea
1-(4-Methoxyphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethoxyphenyl)urea
1-(4-Difluoromethoxyphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethylphenyl)urea
1-(3-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Butylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Acetylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(3-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Fluorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-Phenyl-3-(2-thiophen-2-ylethyl)urea
1-(4-Methylsulfanylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(3-Chloro-4-fluorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Isopropylphenyl)-3-(2-thiophen-2-ylethyl)urea
4-(3-Benzothiazol-6-ylureido)benzoic acid ethyl ester
4-[3-(4-Imidazol-1-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(6-Fluorobenzothiazol-2-yl)ureido]benzoic acid ethyl ester

5-[3-(4-Ethoxycarbonylphenyl)ureido]furan-2-carboxylic acid methyl ester
4-[3-(1H-Indol-6-yl)ureido]benzoic acid ethyl ester
4-[3-(3-Methoxycarbonylphenyl)ureido]benzoic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]thiophene-3-carboxylic acid methyl ester
4-{3-[2-(1-Methyl-1H-pyrrol-2-yl)ethyl]ureido}benzoic acid ethyl ester
4-[3-(6-Methoxypyridin-3-yl)ureido]benzoic acid ethyl ester
6-[3-(4-Ethoxycarbonylphenyl)ureido]nicotinic acid methyl ester
4-[3-(6-Chloropyridin-3-yl)ureido]benzoic acid ethyl ester
4-[3-(4-Carboxymethylphenyl)ureido]benzoic acid ethyl ester
4-[3-(1H-Indol-5-yl)ureido]benzoic acid ethyl ester
4-(3-Benzothiazol-2-ylureido)benzoic acid ethyl ester
4-(3-[1,3,4]Thiadiazol-2-ylureido)benzoic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid ethyl ester
1-(4-Fluorophenyl)-3-(4-morpholin-4-ylphenyl)urea
1-Benzothiazol-6-yl-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(4-imidazol-1-ylphenyl)urea
6-[3-(4-Fluorophenyl)ureido]nicotinic acid methyl ester
1-(6-Chlorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(6-Fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(4,6-Difluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(6-methoxybenzothiazol-2-yl)urea
1-(4-Fluorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl]urea
3-[3-(4-Fluorophenyl)ureido]benzoic acid methyl ester
1-(4-Fluorophenyl)-3-(2-fluorophenyl)urea
3-[3-(4-Fluorophenyl)ureido]benzoic acid ethyl ester
1-(4-Fluoro-3-methylphenyl)-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-pyridin-4-ylurea
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4-[3-(3-Oxazol-5-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylmethylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-[1,2,3]Thiadiazol-4-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Propionylphenyl)ureido]benzoic acid ethyl ester

4-[3-(4-Acetylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Benzoylphenyl)ureido]benzoic acid ethyl ester
4-{3-[4-(4,5-Dihydrooxazol-2-yl)phenyl]ureido}benzoic acid ethyl ester
4-{3-[4-(2-Methylpyrimidin-4-yl)phenyl]ureido}benzoic acid ethyl ester
1-(4-Fluorophenyl)-3-(4-pyrrol-1-ylphenyl)urea
1-(4-Fluorophenyl)-3-(2-methylbenzothiazol-5-yl)urea
1-(4-Fluorophenyl)-3-(3-oxazol-5-ylphenyl)urea
1-(4-Fluorophenyl)-3-(4-propionylphenyl)urea
1-(4-Fluorophenyl)-3-[4-(2-methylpyrimidin-4-yl)phenyl]urea
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid butyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]-4-methyl pyrimidine-5-carboxylic acid ethyl ester
4-[3-(4-Oxazol-5-ylphenyl)ureido]benzoic acid ethyl ester
2-Chloro-4-[3-(4-ethoxycarbonylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]-2-methoxybenzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]-3-methoxybenzoic acid ethyl ester
6-[3-(4-Ethoxycarbonylphenyl)ureido]nicotinic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]-3-hydroxybenzoic acid ethyl ester
4-[3-(3-Acetylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Butyrylphenyl)ureido]benzoic acid ethyl ester
4-{3-[4-(1H-Pyrazol-3-yl)phenyl]ureido}benzoic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid propyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid pentyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid isobutyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid phenyl ester
{4-[3-(4-Fluorophenyl)ureido]phenyl}acetic acid ethyl ester
1-(4-Benzoylphenyl)-3-(4-fluorophenyl)urea
1-(4-Butyrylphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluorophenyl)ureido]benzoic acid butyl ester
2-Chloro-4-[3-(4-fluorophenyl)ureido]benzoic acid ethyl ester
1-(4-Chlorophenyl)-3-(4-trifluoromethylphenyl)urea
1-(4-Chlorophenyl)-3-(4-cyanophenyl)urea
1-(4-Bromo-3-chlorophenyl)-3-(4-chlorophenyl)urea
4-[3-(2-Chlorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Methylsulfanylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Chlorophenyl)ureido]benzoic acid ethyl ester
1-(4-Chlorophenyl)-3-(4-dimethylaminophenyl)urea
1-Phenyl-3-(4-ethoxyphenyl)urea
1-(3-Chlorophenyl)-3-(4-ethoxyphenyl)urea
4-[3-(3-Chlorophenyl)ureido]benzoic acid ethyl ester
4-(3-Phenylureido)benzoic acid methyl ester
1-(3-Methylsulfanyl[1,2,4] thiadiazol-5-yl)-3-phenylurea
1-(3-Ethylsulfanyl[1,2,4] thiadiazol-5-yl)-3-phenylurea

1-(4-Chlorophenyl)-3-(2,3-dihydrobenzo[1,4]dioxan-6-yl)urea
1-(4-Acetylphenyl)-3-(3,4-dichlorophenyl)urea
1-Thiazol-2-yl-3-(4-methylphenyl)urea
5-[3-(4-Chlorophenyl)ureido]-3-methyl thiophene-2-carboxylic acid ethyl ester
{4-[3-(4-Methylsulfanylphenyl)ureido]benzoylamino}acetic acid
1-[5-(2-Methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophen-2-yl]-3-(3-trifluoro methylphenyl)urea
1-(3,4-Dichlorophenyl)-3-(3-hydroxyphenyl)urea
1-[3-(2-Methylpyrimidin-4-yl)phenyl]-3-phenylurea
1-(3-Acetylphenyl)-3-phenylurea
1-(3-Chlorophenyl)-3-(4-methylthiazol-2-yl)urea
1-[2-(4-Fluorophenyl)ethyl]-3-(4-isopropyl phenyl)urea
1-(4-Chlorophenyl)-3-(4-trifluoromethoxyphenyl)urea
1-(4-Chlorophenyl)-3-(4-methanesulfonylphenyl)urea
1-[2-(3-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea
1-[2-(2-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea
1-[2-(3-Fluorophenyl)ethyl]-3-(4-trifluoromethylphenyl)urea
1-(4-Isopropylphenyl)-3-thiazol-2-ylurea
1-(4-Acetylphenyl)-3-(4-bromophenyl)urea
1-(4-Butoxyphenyl)-3-(4-chlorophenyl)urea
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(3-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(4-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl] urea
1-(3,4-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(6-pyrrolidin-1-ylpyridin-2-yl)phenyl] urea
1-(4-Azepan-1-yl-3-fluorophenyl)-3-(4-chlorophenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-pyrrolidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethoxy)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-methoxyethoxy)phenyl] urea
1-(4-Chlorophenyl)-3-[3-(2-isopropylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-[1,4]oxazepan-4-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
4-[3-(3-Fluoro-4-piperidin-1-ylphenyl)ureido]benzoic acid ethyl ester
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methoxyethoxy)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-morpholin-4-ylethoxy)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyridin-3-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(6-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-hydroxypiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyridin-2-yl-phenyl) urea

1-(4-Chlorophenyl)-3-(4-pyridin-4-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(2-piperidin-1-ylpyrimidin-4-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethyl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(2,3-Dihydrobenzofuran-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3,5-Dimethoxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(3-pyrazol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)phenyl] urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(3-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[4-(4,4-difluoropiperidin-1-yl)-3-fluorophenyl] urea
1-(4-Butyrylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(1-Methyl-1H-indazol-5-yl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrazol-1-ylphenyl) urea
1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3,5-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Chloro-4-fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Ethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methyl-2H-pyrazol-3-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-methylpiperidin-1-yl)phenyl] urea
1-Benzo[1,3]dioxol-5-yl-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(2-methylpiperidin-1-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-methoxyphenyl) urea
1-(4-Chloro-2-hydroxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-trifluoromethylpiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-methylpiperidin-1-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-phenoxyphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-phenoxyphenyl) urea
1-(4-Fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-methoxyphenyl) urea
1-(4-Cyanophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chloro-3-trifluoromethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-trifluoromethylphenyl) urea
1-(3-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Chlorophenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(4-Chlorophenyl)-3-(3-dimethylaminophenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-morpholin-4-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-(3-pyrrol-1-ylphenyl) urea

1-(3,5-Dichlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(3-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(3,5-Bis-trifluoromethylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Acetylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(4-Acetylphenyl)-3-[3-(6-methoxypyridin-2-yl)phenyl] urea
1-(4-Acetylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Chloro-4-morpholin-4-ylphenyl)-3-(4-chlorophenyl) urea
1-(4-Chlorophenyl)-3-(4-piperidin-1-ylphenyl) urea
1-(4-Acetylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Butyrylphenyl)-3-(4-piperidin-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chlorophenyl)-3-(1-methyl-1H-indazol-5-yl) urea
1-(3-Acetylphenyl)-3-[2-(4-chlorophenyl)ethyl] urea
1-(4-Chlorophenyl)-3-[3-(2-pyrrolidin-1-ylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyrazol-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-[4-(morpholine-4-carbonyl)phenyl] urea

and pharmaceutically acceptable salts thereof.

Conditions to be treated according to the method of the invention include obesity; psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, depression, cognitive disorders, memory disorders, obsessive compulsive disorders, anorexia, bulimia, attention disorders, epilepsy and related conditions affective and cognitive disorders brought about by disturbances in any of the central monoaminergic systems; and neurological disorders such as Raynaud's syndrome, movement impairment, Parkinson's disease, Huntington's chorea and Alzheimer's disease. Further conditions which may be treated according to the method of the invention include immune, cardiovascular, reproductive and endocrine disorders, endotoxin-induced or cirrhotic hypotension, septic shock, diseases related to the respiratory and gastrointestinal systems such as decreased intestinal motility such as Paralytic ileus caused by peritonitis, surgery, or other noxious situations, extended abuse, addiction and relapse indications such as tobacco smoking, heroin addiction, relapse to cocaine-seeking, and alcoholism.

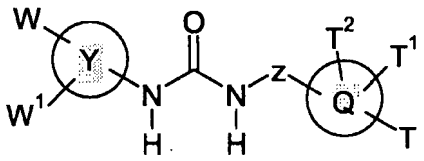
The condition to be treated according to the methods of the invention is preferably obesity.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

CB-1 receptor modulator compounds for use in the methods of the invention include CB-1 antagonists.

Certain compounds of formula (I) are novel.

The present invention also provides a compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein:

Y is phenyl, a 5- or 6-membered heteroaryl group, or a 9-membered bicyclic heteroaryl group attached to the urea through the 5-membered ring;

W is $COOR^1$, COR^1, C_{1-6}alkoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkoxy, $-(CH_2)_m-NR^2R^3$, $-O(CH_2)_n-NR^2R^3$, C_{1-6}alkylthio, fluoro, chloro or 5- or 6-membered heteroaryl optionally substituted by C_{1-3}alkyl;

W^1 is hydrogen, halogen or C_{1-3}alkoxy;

Z is C_{1-3}alkylene, C_{2-3}alkenylene or a bond;

Q is phenyl, pyridyl or a 9-membered bicyclic heteroaryl group;

T is halogen, $COOR^1$, COR^1, C_{1-6}alkyl, C_{1-6}alkylthio, $-(CH_2)_m-NR^2R^3$, or a 5- to 10-membered heteroaryl group optionally substituted by C_{1-3}alkyl; or when Z is C_{1-3}alkylene or C_{2-3}alkenylene, then T may be hydrogen;

T^1 and T^2 are independently selected from hydrogen, halogen and hydroxy;

R^1 is C_{1-6}alkyl or phenyl or a 5- or 6-membered heteroaryl or heterocyclyl group;

R^2 and R^3 together with the nitrogen to which they are attached form a 5- to 7-membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and NR^4, and optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy;

m is 0, 1, 2 or 3; and

n is 2 or 3;

provided that the compound is not:

1-Benzo[b]thiophen-2-yl-3-(2-methylphenyl)urea,

4-[3-(2-Chlorophenyl)ureido]benzoic acid ethyl ester,

4-[3-(4-Methylsulfanylphenyl)ureido]benzoic acid ethyl ester,

4-[3-(4-Chlorophenyl)ureido]benzoic acid ethyl ester,

1-(3-Chlorophenyl)-3-(4-ethoxyphenyl)urea,

4-[3-(3-Chlorophenyl)ureido]benzoic acid ethyl ester,

1,3-Bis(4-acetylphenyl)urea,

4-[3-(4-Fluorophenyl)ureido]benzoic acid ethyl ester,

1-(4-Fluorophenyl)-3-(4-methoxyphenyl)urea,

1-(4-Acetylphenyl)-3-(3-chlorophenyl)urea,

1-(4-Acetylphenyl)-3-(4-chlorophenyl)urea,

1-(4-Chlorophenyl)-3-(4-ethoxyphenyl)urea,

1-(4-Acetylphenyl)-3-(4-fluorophenyl)urea,

4-[3-(4-Fluorophenyl)ureido]benzoic acid methyl ester,

4-[3-(3-Fluorophenyl)ureido]benzoic acid ethyl ester,

4-[3-(2-Fluorophenyl)ureido]benzoic acid ethyl ester,

1-(3-Ethoxyphenyl)-3-(4-fluorophenyl)urea,

1-(4-Chlorophenyl)-3-(4-trifluoromethoxyphenyl)urea,

1-(3-Acetylphenyl)-3-[2-(4-chlorophenyl)ethyl]urea, or

1-(4-Chlorophenyl)-3-[4-(morpholine-4-carbonyl)phenyl]urea.

The molecular weight of the compounds of formula (Ia) is preferably less than 800, more preferably less than 600.

As far as they are appropriate the preferences given for variables in the compounds of formula (I) recited above are also applicable to the compounds of formula (Ia).

In the compounds of formula (Ia):

Particular examples of 5- or 6-membered heteroaryl groups that Y may represent include thienyl, thiazolyl and thiadiazolyl.

Particular examples of 9-membered bicyclic heteroaryl groups that Y and Q may represent include benzothienyl and benzothiazolyl, especially benzothien-2-yl and benzothiazol-2-yl.

A specific group of compounds of formula (Ia) which may be mentioned are those where Y is phenyl.

When Y is phenyl, W is preferably $COOR^1$ especially COOEt, or COR^1, C_{1-6}alkoxy, C_{1-6}alkylthio, fluoro, chloro, C_{1-3}alkoxyC_{1-3}alkoxy, $-(CH_2)_m-NR^2R^3$, $-O(CH_2)_n-NR^2R^3$, or 5- or 6-membered heteroaryl optionally substituted by C_{1-3}alkyl. Particular W groups which may be mentioned are chloro, C_{1-3}alkoxyC_{1-3}alkoxy, $-(CH_2)_m-NR^2R^3$ and $-O(CH_2)_n-NR^2R^3$ where $-NR^2R^3$, is preferably morpholinyl.

Heteroaryl groups which W may represent include 5- or 6-membered heteroaryl groups containing 1 or 2 nitrogen atoms such as pyrazole, pyrrole, imidazole, pyrimidine or pyridine.

W^1 is preferably hydrogen, halogen or C_{1-3}alkoxy, more preferably hydrogen.

W^1 is preferably hydrogen.

Z is preferably C_2alkylene, C_2alkenylene or a bond, more preferably C_2alkylene or a bond, especially a bond.

A specific group of compounds of formula (Ia) which may be mentioned are those where Q is phenyl.

A group of compounds of formula (Ia) which may be mentioned are those where T is halogen, $COOR^1$, COR^1, C_{1-6}alkyl, C_{1-6}alkylthio, or a 5- or 6-membered heteroaryl group optionally substituted by C_{1-3}alkyl; or when Z is C_{1-3}alkylene or C_{2-3}alkenylene, then T may be hydrogen.

T is preferably halogen, $COOR^1$, COR^1, C_{1-6}alkyl, $-(CH_2)_m-NR^2R^3$ optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy, or a 5- to 10-membered heteroaryl group optionally substituted by C_{1-3}alkyl, e.g. a 5- or 6-membered heteroaryl group containing 1 or 2 nitrogen atoms such as pyrazole, pyrrole, imidazole, pyrimidine or pyridine, or thiazole, thiadiazole, oxazole or 3,4-dihydro-1H-isoquinolin-2-yl.

T^1 and T^2 are preferably hydrogen, halogen or hydroxy, more preferably hydrogen or halogen.

T^2 is preferably hydrogen.

A specific group of compounds which may be mentioned are those where T is $-(CH_2)_m-NR^2R^3$, T^1 is halogen, e.g. fluoro, and T^2 is hydrogen.

When T is $-(CH_2)_m-NR^2R^3$, m is preferably 0 and R^2 and R^3 together with the nitrogen to which they are attached preferably form a 5- to 7-membered heterocyclic ring, e.g. a piperidine ring, optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy, e.g. methyl.

W and T are preferably different.

Preferably at least one of Y and Q is phenyl.

A group of compounds of formula (Ia) which may be mentioned are those where R^1 is C_{1-6}alkyl or phenyl or a 5- or 6-membered heteroaryl group.

The present invention also provides a compound selected from:

2-[3-(4-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
2-[3-(3-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
4-Methyl-2-[3-(4-methylsulfanylphenyl)ureido]thiazole-5-carboxylic acid ethyl ester
1-(4-Acetylphenyl)-3-benzo[b]thiophen-2-ylurea
1-Benzo[b]thiophen-2-yl-3-(4-methanesulfonylphenyl)urea
4-[3-(4-Fluoro-2-methylphenyl)ureido]benzoic acid ethyl ester
4-[3-(2,4,6-Trifluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(2,4-Difluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(3,4-Difluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(2-Chloro-4-fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluoro-3-methylphenyl)ureido]benzoic acid ethyl ester
4-[3-(3-Chloro-4-fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluoro-3-methoxyphenyl)ureido]benzoic acid ethyl ester
1-(4-Ethoxyphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluorophenyl)ureido]-3-methylbenzoic acid methyl ester
4-[3-(4-Fluorophenyl)ureido]-3-hydroxybenzoic acid methyl ester
1-(2-Thiophen-2-ylethyl)-3-(4-methylphenyl)urea
1-(4-Methoxyphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethoxyphenyl)urea
1-(4-Difluoromethoxyphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethylphenyl)urea
1-(3-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Butylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Acetylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(3-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Fluorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea

1-(4-Methylsulfanylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Isopropylphenyl)-3-(2-thiophen-2-ylethyl)urea
4-(3-Benzothiazol-6-ylureido)benzoic acid ethyl ester
4-[3-(4-Imidazol-1-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(6-Fluorobenzothiazol-2-yl)ureido]benzoic acid ethyl ester
5-[3-(4-Ethoxycarbonylphenyl)ureido]furan-2-carboxylic acid methyl ester
4-[3-(1H-Indol-6-yl)ureido]benzoic acid ethyl ester
4-[3-(3-Methoxycarbonylphenyl)ureido]benzoic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]thiophene-3-carboxylic acid methyl ester
4-{3-[2-(1-Methyl-1H-pyrrol-2-yl)ethyl]ureido}benzoic acid ethyl ester
4-[3-(6-Methoxypyridin-3-yl)ureido]benzoic acid ethyl ester
6-[3-(4-Ethoxycarbonylphenyl)ureido]nicotinic acid methyl ester
4-[3-(6-Chloropyridin-3-yl)ureido]benzoic acid ethyl ester
4-[3-(4-Carboxymethylphenyl)ureido]benzoic acid ethyl ester
4-[3-(1H-Indol-5-yl)ureido]benzoic acid ethyl ester
1-(4-Fluorophenyl)-3-(4-morpholin-4-ylphenyl)urea
1-Benzothiazol-6-yl-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(4-imidazol-1-ylphenyl)urea
6-[3-(4-Fluorophenyl)ureido]nicotinic acid methyl ester
1-(6-Chlorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(6-Fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(4,6-Difluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(6-methoxybenzothiazol-2-yl)urea
1-(4-Fluorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl]urea
3-[3-(4-Fluorophenyl)ureido]benzoic acid methyl ester
1-(4-Fluorophenyl)-3-(2-fluorophenyl)urea
3-[3-(4-Fluorophenyl)ureido]benzoic acid ethyl ester
1-(4-Fluoro-3-methylphenyl)-3-(4-fluorophenyl)urea
4-{3-[3-(2-Methylpyrimidin-4-yl)phenyl]ureido}benzoic acid ethyl ester
4-[3-(1-Oxoindan-5-yl)ureido]benzoic acid ethyl ester
4-[3-(6-Morpholin-4-ylpyridin-3-yl)ureido]benzoic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]thiazole-5-carboxylic acid methyl ester
4-[3-(3-Ethoxycarbonylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid propyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid pentyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid isobutyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid phenyl ester
4-{3-[4-(1,1,2,2-Tetrafluoroethoxy)phenyl]ureido}benzoic acid ethyl ester
4-[3-(3-Oxazol-5-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylmethylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-[1,2,3]Thiadiazol-4-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Propionylphenyl)ureido]benzoic acid ethyl ester

4-[3-(4-Acetylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Benzoylphenyl)ureido]benzoic acid ethyl ester
4-{3-[4-(4,5-Dihydrooxazol-2-yl)phenyl]ureido}benzoic acid ethyl ester
4-{3-[4-(2-Methylpyrimidin-4-yl)phenyl]ureido}benzoic acid ethyl ester
1-(4-Fluorophenyl)-3-(4-pyrrol-1-ylphenyl)urea
1-(4-Fluorophenyl)-3-(2-methylbenzothiazol-5-yl)urea
1-(4-Fluorophenyl)-3-(3-oxazol-5-ylphenyl)urea
1-(4-Fluorophenyl)-3-(4-propionylphenyl)urea
1-(4-Fluorophenyl)-3-[4-(2-methylpyrimidin-4-yl)phenyl]urea
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid butyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]-4-methylpyrimidine-5-carboxylic acid ethyl ester
4-[3-(4-Oxazol-5-ylphenyl)ureido]benzoic acid ethyl ester
2-Chloro-4-[3-(4-ethoxycarbonylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]-2-methoxybenzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]-3-methoxybenzoic acid ethyl ester
6-[3-(4-Ethoxycarbonylphenyl)ureido]nicotinic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]-3-hydroxybenzoic acid ethyl ester
4-[3-(3-Acetylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Butyrylphenyl)ureido]benzoic acid ethyl ester
4-{3-[4-(1H-Pyrazol-3-yl)phenyl]ureido}benzoic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid propyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid pentyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid isobutyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid phenyl ester
{4-[3-(4-Fluorophenyl)ureido]phenyl}acetic acid ethyl ester
1-(4-Benzoylphenyl)-3-(4-fluorophenyl)urea
1-(4-Butyrylphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluorophenyl)ureido]benzoic acid butyl ester
2-Chloro-4-[3-(4-fluorophenyl)ureido]benzoic acid ethyl ester
1-[2-(3-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea
1-[2-(2-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea
1-[2-(3-Fluorophenyl)ethyl]-3-(4-trifluoromethylphenyl)urea
1-(4-Isopropylphenyl)-3-thiazol-2-ylurea
1-(4-Acetylphenyl)-3-(4-bromophenyl)urea
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(3-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(4-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl] urea
1-(3,4-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(6-pyrrolidin-1-ylpyridin-2-yl)phenyl] urea
1-(4-Azepan-1-yl-3-fluorophenyl)-3-(4-chlorophenyl) urea

1-(4-Chlorophenyl)-3-(3-fluoro-4-pyrrolidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethoxy)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-methoxyethoxy)phenyl] urea
1-(4-Chlorophenyl)-3-[3-(2-isopropylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-[1,4]oxazepan-4-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
4-[3-(3-Fluoro-4-piperidin-1-ylphenyl)ureido]benzoic acid ethyl ester
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methoxyethoxy)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-morpholin-4-ylethoxy)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyridin-3-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(6-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-hydroxypiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyridin-2-yl-phenyl) urea
1-(4-Chlorophenyl)-3-(4-pyridin-4-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(2-piperidin-1-ylpyrimidin-4-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethyl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(2,3-Dihydrobenzofuran-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3,5-Dimethoxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(3-pyrazol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)phenyl] urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(3-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[4-(4,4-difluoropiperidin-1-yl)-3-fluorophenyl] urea
1-(4-Butyrylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(1-Methyl-1H-indazol-5-yl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrazol-1-ylphenyl) urea
1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3,5-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Chloro-4-fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Ethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methyl-2H-pyrazol-3-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-methylpiperidin-1-yl)phenyl] urea
1-Benzo[1,3]dioxol-5-yl-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(2-methylpiperidin-1-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-methoxyphenyl) urea
1-(4-Chloro-2-hydroxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-trifluoromethylpiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-methylpiperidin-1-yl)phenyl] urea

1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-phenoxyphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-phenoxyphenyl) urea
1-(4-Fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-methoxyphenyl) urea
1-(4-Cyanophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chloro-3-trifluoromethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-trifluoromethylphenyl) urea
1-(3-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Chlorophenyl)-3-(3-dimethylaminophenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-morpholin-4-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-(3-pyrrol-1-ylphenyl) urea
1-(3,5-Dichlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(3-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(3,5-Bis-trifluoromethylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Acetylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(4-Acetylphenyl)-3-[3-(6-methoxypyridin-2-yl)phenyl] urea
1-(4-Acetylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Chloro-4-morpholin-4-ylphenyl)-3-(4-chlorophenyl) urea
1-(4-Chlorophenyl)-3-(4-piperidin-1-ylphenyl) urea
1-(4-Acetylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Butyrylphenyl)-3-(4-piperidin-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chlorophenyl)-3-(1-methyl-1H-indazol-5-yl) urea
1-(4-Chlorophenyl)-3-[3-(2-pyrrolidin-1-ylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyrazol-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-[4-(morpholine-4-carbonyl)phenyl] urea

and pharmaceutically acceptable salts thereof.

As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkylene, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl and the like. "Alkenyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond. As used herein, for example, "C_{1-6}alkyl" is used to mean an alkyl having 1-6 carbons, i.e. 1, 2, 3, 4, 5 or 6 carbons in a straight or branched configuration.

C_{1-3}Fluoroalkyl and C_{1-3}fluoroalkoxy include groups where one or more hydrogen atoms are replaced by fluorine, e.g. $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$ and $-OCF_2CHF_2$.

The term "halogen" includes fluorine, chlorine, bromine, and iodine atoms, especially fluorine and chlorine atoms.

Unless otherwise stated, the term "heterocyclyl" includes 5- to 7-membered, particularly 5- and 6-membered, saturated and partially saturated rings containing one or two heteroatoms chosen from oxygen, sulfur, and nitrogen. The heteroatoms are not directly attached to one another. Examples of heterocyclic rings include oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, morpholine, 4,5-dihydrooxazole and the like. Other examples of heterocyclic rings include the oxidised forms of the sulfur-containing rings. Thus, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1,1-dioxide, tetrahydrothiopyran 1-oxide, and tetrahydrothiopyran 1,1-dioxide are also considered to be heterocyclic rings.

Unless otherwise stated, the term "heteroaryl" includes mono- and bicyclic 5- to 10-membered heteroaryl rings containing 1–4 heteroatoms chosen from oxygen, sulfur, and nitrogen. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. Bicyclic heteroaryl groups include bicyclic heteroaromatic groups where a 5- or 6-membered heteroaryl ring is fused to a phenyl or another heteroaromatic group. Examples of such bicyclic heteroaromatic rings are benzofuran, benzothiophene, indole, benzoxazole, benzothiazole, indazole, benzimidazole, benzotriazole, quinoline, isoquinoline, quinazoline, quinoxaline and purine. Bicyclic heteroaryl groups also include groups formed from a fused aromatic ring and a saturated or partially saturated ring, for example 3,4-dihydro-1H-isoquinoline or 2,3-dihydrobenzofuran.

The above formulae are shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers, e.g. geometric isomers, optical isomers, diastereoisomers, etc, and pharmaceutically acceptable salts thereof, except where specifically drawn or stated otherwise. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included, except where specifically drawn or stated otherwise. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers. The different isomeric forms may be separated or resolved from one another by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. When an isomeric form of a compound is provided substantially free from other isomers, it will preferably contain less than 5% w/w, more preferably less than 2% w/w and especially less than 1% w/w of the other isomers.

When a tautomer of the compound of the above formulae exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of the above formulae and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N',N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylameine, trimethylamine, tripropylamine, tromethamine and the like.

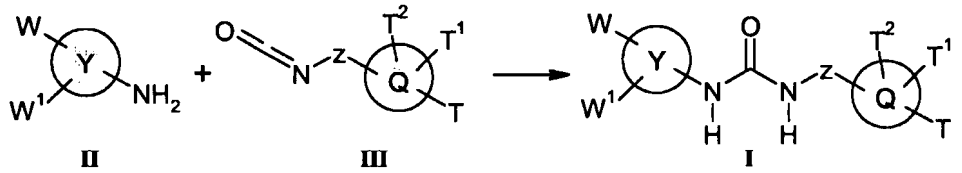
When the compound of the invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like.

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure especially at least 98% pure (% are on a weight for weight basis).

In accordance with this invention, the compounds of formula (I) can be prepared as illustrated in the schemes below:

Compounds of formula (I) can be readily prepared by combining an amine of formula (II) with an isocyanate of formula (III) in a suitable solvent, at a temperature of typically between 20°C and 100°C (Scheme 1). An example of a suitable solvent is toluene. Compounds of formulae (II) and (III) are generally commercially available or readily synthesised using known techniques.

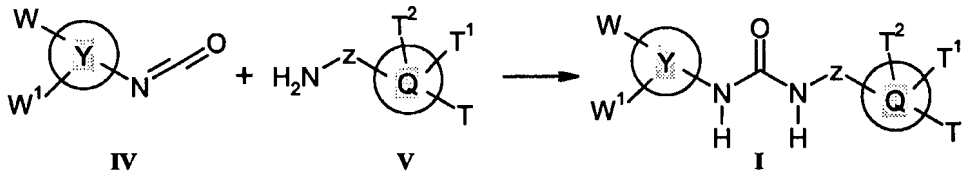
Scheme 1



II III I

Compounds of formula (I) can alternatively be prepared by combining an amine of formula (IV) with an isocyanate of formula (V) using the conditions described above (Scheme 2). Compounds of formulae (IV) and (V) are generally commercially available or readily synthesised using known techniques.

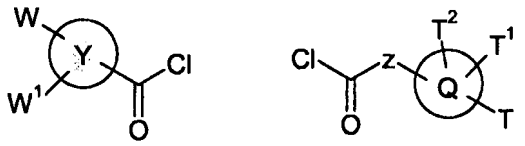
Scheme 2



IV V I

Synthesis of non-commercial isocyanates of formula (III) or (IV) can be achieved, for example, from an acid chloride of formulae (VI) or (VII) (Figure 1) by treatment with sodium azide in a suitable solvent such as tetrahydrofuran and water. The resulting acylazide is then heated in a suitable solvent such as toluene. Acid chlorides of formulae (VI) and (VII) are typically commercially available or readily synthesised for the corresponding carboxylic acid using known techniques. Examples of isocyantes that may be synthesised using this process include compounds of formula (IV) where Y = benzothiophene, and compounds of formula (III) where Z = alkenylene. The isocyantes can be used *in situ* and reacted with a suitable amine to provide compounds of formula (I) as described above.

Figure 1



VI VII

Amines of formulae (II) and (V) may also be prepared from compounds of formulae (VI) and (VII). The corresponding isocyanates are prepared under condition described above and then hydrolysed using water to give the corresponding amines of formulae (II) and (V).

Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

Any novel intermediates of use in the preparation of the compounds of formula (I) are also encompassed by the present invention.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

As indicated above the compounds of formula (I) are useful for the treatment of conditions associated with the CB-1 receptor, in particular obesity. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

Certain of the compounds of formula (I) have not previously been disclosed as having pharmaceutical utility.

The invention also provides a pharmaceutical composition comprising a compound of formula (Ia) or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

The invention also provides a pharmaceutical composition comprising a compound selected from:

2-[3-(4-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
2-[3-(3-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
4-Methyl-2-[3-(4-methylsulfanylphenyl)ureido]thiazole-5-carboxylic acid ethyl ester
1-(4-Acetylphenyl)-3-benzo[b]thiophen-2-ylurea
1-Benzo[b]thiophen-2-yl-3-(4-methanesulfonylphenyl)urea
4-[3-(4-Fluoro-2-methylphenyl)ureido]benzoic acid ethyl ester
4-[3-(2,4,6-Trifluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(2,4-Difluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(3,4-Difluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(2-Chloro-4-fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluoro-3-methylphenyl)ureido]benzoic acid ethyl ester
4-[3-(3-Chloro-4-fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluoro-3-methoxyphenyl)ureido]benzoic acid ethyl ester
1-(4-Ethoxyphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluorophenyl)ureido]-3-methylbenzoic acid methyl ester
4-[3-(4-Fluorophenyl)ureido]-3-hydroxybenzoic acid methyl ester
1-(2-Thiophen-2-ylethyl)-3-(4-methylphenyl)urea
1-(4-Methoxyphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethoxyphenyl)urea
1-(4-Difluoromethoxyphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea

1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethylphenyl)urea
1-(3-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Butylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Acetylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(3-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Fluorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Methylsulfanylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Isopropylphenyl)-3-(2-thiophen-2-ylethyl)urea
4-(3-Benzothiazol-6-ylureido)benzoic acid ethyl ester
4-[3-(4-Imidazol-1-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(6-Fluorobenzothiazol-2-yl)ureido]benzoic acid ethyl ester
5-[3-(4-Ethoxycarbonylphenyl)ureido]furan-2-carboxylic acid methyl ester
4-[3-(1H-Indol-6-yl)ureido]benzoic acid ethyl ester
4-[3-(3-Methoxycarbonylphenyl)ureido]benzoic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]thiophene-3-carboxylic acid methyl ester
4-{3-[2-(1-Methyl-1H-pyrrol-2-yl)ethyl]ureido}benzoic acid ethyl ester
4-[3-(6-Methoxypyridin-3-yl)ureido]benzoic acid ethyl ester
6-[3-(4-Ethoxycarbonylphenyl)ureido]nicotinic acid methyl ester
4-[3-(6-Chloropyridin-3-yl)ureido]benzoic acid ethyl ester
4-[3-(4-Carboxymethylphenyl)ureido]benzoic acid ethyl ester
4-[3-(1H-Indol-5-yl)ureido]benzoic acid ethyl ester
1-(4-Fluorophenyl)-3-(4-morpholin-4-ylphenyl)urea
1-Benzothiazol-6-yl-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(4-imidazol-1-ylphenyl)urea
6-[3-(4-Fluorophenyl)ureido]nicotinic acid methyl ester
1-(6-Chlorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(6-Fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(4,6-Difluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(6-methoxybenzothiazol-2-yl)urea
1-(4-Fluorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl]urea
3-[3-(4-Fluorophenyl)ureido]benzoic acid methyl ester
1-(4-Fluorophenyl)-3-(2-fluorophenyl)urea
3-[3-(4-Fluorophenyl)ureido]benzoic acid ethyl ester
1-(4-Fluoro-3-methylphenyl)-3-(4-fluorophenyl)urea
4-{3-[3-(2-Methylpyrimidin-4-yl)phenyl]ureido}benzoic acid ethyl ester
4-[3-(1-Oxoindan-5-yl)ureido]benzoic acid ethyl ester
4-[3-(6-Morpholin-4-ylpyridin-3-yl)ureido]benzoic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]thiazole-5-carboxylic acid methyl ester
4-[3-(3-Ethoxycarbonylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid propyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid pentyl ester

4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid isobutyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid phenyl ester
4-{3-[4-(1,1,2,2-Tetrafluoroethoxy)phenyl]ureido}benzoic acid ethyl ester
4-[3-(3-Oxazol-5-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylmethylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-[1,2,3]Thiadiazol-4-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Propionylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Acetylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Benzoylphenyl)ureido]benzoic acid ethyl ester
4-{3-[4-(4,5-Dihydrooxazol-2-yl)phenyl]ureido}benzoic acid ethyl ester
4-{3-[4-(2-Methylpyrimidin-4-yl)phenyl]ureido}benzoic acid ethyl ester
1-(4-Fluorophenyl)-3-(4-pyrrol-1-ylphenyl)urea
1-(4-Fluorophenyl)-3-(2-methylbenzothiazol-5-yl)urea
1-(4-Fluorophenyl)-3-(3-oxazol-5-ylphenyl)urea
1-(4-Fluorophenyl)-3-(4-propionylphenyl)urea
1-(4-Fluorophenyl)-3-[4-(2-methylpyrimidin-4-yl)phenyl]urea
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid butyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]-4-methyl pyrimidine-5-carboxylic acid ethyl ester
4-[3-(4-Oxazol-5-yl phenyl)ureido]benzoic acid ethyl ester
2-Chloro-4-[3-(4-ethoxycarbonylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]-2-methoxybenzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]-3-methoxybenzoic acid ethyl ester
6-[3-(4-Ethoxycarbonylphenyl)ureido]nicotinic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]-3-hydroxy benzoic acid ethyl ester
4-[3-(3-Acetylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Butyrylphenyl)ureido]benzoic acid ethyl ester
4-{3-[4-(1H-Pyrazol-3-yl)phenyl]ureido}benzoic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid propyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid pentyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid isobutyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid phenyl ester
{4-[3-(4-Fluorophenyl)ureido]phenyl}acetic acid ethyl ester
1-(4-Benzoylphenyl)-3-(4-fluorophenyl)urea
1-(4-Butyrylphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluorophenyl)ureido]benzoic acid butyl ester
2-Chloro-4-[3-(4-fluorophenyl)ureido]benzoic acid ethyl ester
1-[2-(3-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea
1-[2-(2-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea
1-[2-(3-Fluorophenyl)ethyl]-3-(4-trifluoromethylphenyl)urea
1-(4-Isopropylphenyl)-3-thiazol-2-ylurea
1-(4-Acetylphenyl)-3-(4-bromophenyl)urea
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea

1-(4-Chlorophenyl)-3-(3-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(4-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl] urea
1-(3,4-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(6-pyrrolidin-1-ylpyridin-2-yl)phenyl] urea
1-(4-Azepan-1-yl-3-fluorophenyl)-3-(4-chlorophenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-pyrrolidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethoxy)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-methoxyethoxy)phenyl] urea
1-(4-Chlorophenyl)-3-[3-(2-isopropylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-[1,4]oxazepan-4-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
4-[3-(3-Fluoro-4-piperidin-1-ylphenyl)ureido]benzoic acid ethyl ester
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methoxyethoxy)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-morpholin-4-ylethoxy)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyridin-3-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(6-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-hydroxypiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyridin-2-yl-phenyl) urea
1-(4-Chlorophenyl)-3-(4-pyridin-4-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(2-piperidin-1-ylpyrimidin-4-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethyl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(2,3-Dihydrobenzofuran-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3,5-Dimethoxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(3-pyrazol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)phenyl] urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(3-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[4-(4,4-difluoropiperidin-1-yl)-3-fluorophenyl] urea
1-(4-Butyrylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(1-Methyl-1H-indazol-5-yl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrazol-1-ylphenyl) urea
1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3,5-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Chloro-4-fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Ethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methyl-2H-pyrazol-3-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-methylpiperidin-1-yl)phenyl] urea

1-Benzo[1,3]dioxol-5-yl-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(2-methylpiperidin-1-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-methoxyphenyl) urea
1-(4-Chloro-2-hydroxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-trifluoromethylpiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-methylpiperidin-1-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-phenoxyphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-phenoxyphenyl) urea
1-(4-Fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-methoxyphenyl) urea
1-(4-Cyanophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chloro-3-trifluoromethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-trifluoromethylphenyl) urea
1-(3-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Chlorophenyl)-3-(3-dimethylaminophenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-morpholin-4-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-(3-pyrrol-1-ylphenyl) urea
1-(3,5-Dichlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(3-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(3,5-Bis-trifluoromethylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Acetylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(4-Acetylphenyl)-3-[3-(6-methoxypyridin-2-yl)phenyl] urea
1-(4-Acetylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Chloro-4-morpholin-4-ylphenyl)-3-(4-chlorophenyl) urea
1-(4-Chlorophenyl)-3-(4-piperidin-1-ylphenyl) urea
1-(4-Acetylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Butyrylphenyl)-3-(4-piperidin-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chlorophenyl)-3-(1-methyl-1H-indazol-5-yl) urea
1-(4-Chlorophenyl)-3-[3-(2-pyrrolidin-1-ylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyrazol-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-[4-(morpholine-4-carbonyl)phenyl] urea

or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Moreover, within this preferred embodiment, the invention encompasses a pharmaceutical composition for the treatment of disease by modulating the CB-1 receptor, resulting in the suppression of appetite, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions of the present invention, or administered by the methods of the present invention, comprise a compound of formula (I) or a pharmaceutically acceptable salt thereof, as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous). Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions may include a pharmaceutically acceptable carrier and a compound of formula (I), or a pharmaceutically acceptable salt thereof. The compounds of formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of the invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient. For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices.

These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compositions of the present invention or used in the present invention are effective to suppress appetite, to prophylactically prevent overweight, to assist in regulating food intake, to assist as a diet aid, and to treat obesity. Generally, dosage levels on the order of from about 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, obesity may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

Materials and methods:

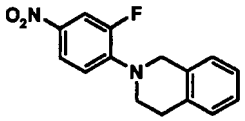
Column chromatography was carried out on SiO_2 (40–63 mesh). LCMS data were obtained using a Waters Symmetry 3.5μ C_{18} column (2.1 × 30.0mm, flow rate = 0.8mL/min) eluting with a (5% MeCN in H_2O)–MeCN solution containing 0.1% HCO_2H over 6min and UV detection at 220nm. Gradient information: 0.0–1.2min: 100% (5% MeCN in H_2O); 1.2–

3.8min: Ramp up to 10% (5% MeCN in H_2O)–90% MeCN; 3.8–4.4min: Hold at 10% (5% MeCN in H_2O)–90% MeCN; 4.4–5.5min: Ramp up to 100% MeCN; 5.5–6.0min: Return to 100% (5% MeCN in H_2O). The mass spectra were obtained employing an electrospray ionisation source in the positive (ES^+) ion mode. Prep HPLC purification was carried out using a Lunar 10μ ODS2 (250 x 21.2mm; Flow rate = 20mL/min) eluting with solvent A (0.05% TFA, 10% MeCN, 90% water) and solvent B (0.05% TFA, 90% MeCN, 10% water) and UV detection at 215 nm. Gradient information: 0.0–0.2 min: 90% A, 10% B; 0.2–10.0 min: Ramp up to 10% A, 90% B; 10.0–15.0 min: 10% A, 90% B; 15.0–16.0 min: Return to 90% A, 10% B.

Abbreviations and acronyms: MeCN: Acetonitrile; DME: Dimethylether; DIPEA: *N,N*-Diisopropylethylamine; DMF: *N,N*-Dimethylformamide; Et_2O: Diethyl ether; EtOAc: Ethyl acetate; EtOH: Ethanol; MeOH: Methanol; PS: Polymer supported; rt: room temperature RT: Retention time; THF: Tetrahydrofuran; TFA: Trifluoroacetic acid; Et_3N: Triethylamine.

PREPARATION 1

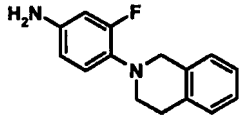
2-(2-Fluoro-4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline



To a solution of 3,4-difluoronitrobenzene (5 g, 31.4 mmol) in EtOAc (50 mL) was added 1,2,3,4-tetrahydroisoquinoline (4.60 g, 34.5 mmol) and Et_3N (4.79 mL, 34.5 mmol) and refluxed for 3h. The reaction mixture was cooled to rt and washed with sodium carbonate (20mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound: δ_H (CD_3OD): 2.97 (2H, t), 3.68 (2H, t), 4.57 (2H, s), 7.19-7.23 (5H, m), 8.01-8.05 (2H, m).

PREPARATION 2

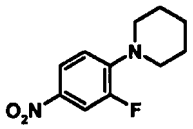
4-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-fluorophenylamine



To a solution of 2-(2-fluoro-4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (2.5 g, 9.18 mmol) in ethanol (220 mL) and THF (15 mL) was added palladium (10%) on activated carbon (973 mg, 0.92 mmol) and stirred under an atmosphere of hydrogen at rt for 18h. The reaction mixture was filtered through celite and concentrated *in vacuo* to yield the title compound: RT = 2.49 min; *m/z* (ES^+) = 243.1 $[M + H]^+$.

PREPARATION 3

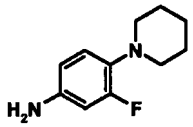
1-(2-Fluoro-4-nitrophenyl)piperidine



Prepared using the method outlined for Preparation 1 using piperidine as the amine: δ_H (DMSO): 1.58-1.67 (6H, m), 3.26-3.29 (4H, m), 7.12-7.16 (1H, m), 7.94-7.80 (2H, m).

PREPARATION 4

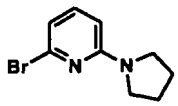
3-Fluoro-4-piperidin-1-ylphenylamine



Prepared from reduction of 1-(2-fluoro-4-nitrophenyl) piperidine using the method outlined in Preparation 2 to give the title compound: δ_H (DMSO): 1.43-1.49 (2H, m), 1.57-1.62 (4H, m), 2.75-2.77 (4H, t), 4.92 (2H, s), 6.27-6.34 (2H, m), 6.72-6.77 (1H, m).

PREPARATION 5

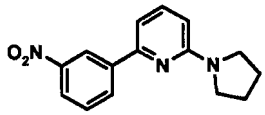
2-Bromo-6-pyrrolidin-1-ylpyridine



A mixture of 2,6-dibromopyridine (5.00 g, 21.10 mmol) and pyrrolidine (10 mL) was stirred for 20h. The reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ (aq), the organic phase was dried ($MgSO_4$) and the solvent was removed under vacuum. The resulting solid was recrystallised (MeOH) to give the title compound: RT = 3.84 min; *m/z* (ES^+) = 227.04 $[M + H]^+$.

PREPARATION 6

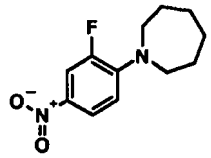
2-(3-Nitrophenyl)-6-pyrrolidin-1-yl pyridine



Argon was bubbled through a mixture of 3-nitrophenylboronic acid (1.22 g, 7.30 mmol), 2-bromo-6-pyrrolidin-1-yl pyridine (1.50 g, 6.64 mmol) and $NaHCO_3$ (1.67 g, 19.91 mmol) in DME (60 mL) and water (25 mL) for 15min. $Pd(Ph_3)_4$ (0.64 g, 0.553 mmol) was added and the reaction refluxed under argon for 4h. The solvent was removed under vacuum and the resulting residue purified by flash chromatography (SiO_2, eluting with 20:80, 40:60 then 60:40 CH_2Cl_2, *i*-hexane) to give the title compound: RT = 3.45 min; *m/z* (ES^+) = 270.16 $[M + H]^+$.

PREPARATION 7

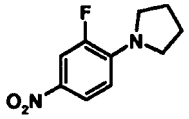
1-(2-Fluoro-4-nitrophenyl)azepane



A solution of 3,4-difluoronitrobenzene (0.20 g, 1.26 mmol), homopiperidine (0.14 g, 1.38 mmol) and Et_3N (0.14 g, 1.38 mmol) in EtOAc (2 mL) was heated at 80°C for 20h. Homopiperidine (0.14 g, 1.38 mmol) was added and the reaction heated at 80°C for 4h. The solid was purified using an SPE cartridges (SCX, eluting with MeOH) to give the title compound: RT = 4.17 min; *m/z* (ES^+) = 239.04 $[M + H]^+$.

PREPARATION 8

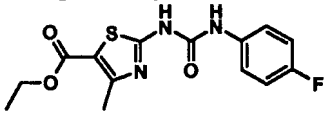
1-(2-Fluoro-4-nitrophenyl)pyrrolidine



A solution of 3,4-difluoronitrobenzene (0.20 g, 1.26 mmol), pyrrolidine (98 mg, 1.38 mmol) and Et_3N (0.14 g, 1.38 mmol) in EtOAc (2 mL) was heated at 80°C for 20h. Pyrrolidine (98 mg, 1.38 mmol) was added and the reaction heated at 80°C for 4h. The solid was purified using an SPE cartridge (SCX, eluting with MeOH) to give the title compound: RT = 3.84 min; *m/z* (ES^+) = 211.01 $[M + H]^+$.

EXAMPLE 1

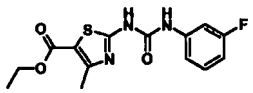
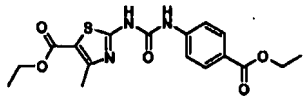
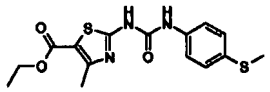
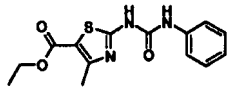
2-[3-(4-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester



A mixture of ethyl (2-amino-4-methylthiazole)-5-carboxylate (60 mg, 0.32 mmol) and 4-fluorophenyl isocyanate (48 mg, 0.35 mmol) in toluene (5mL) was stirred for 20h at 20°C. The precipitate was collected by filtration to give the title compound: RT = 3.86 min; *m/z* (ES^+) = 324.1 $[M + H]^+$.

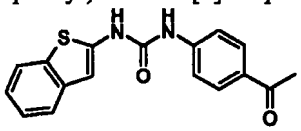
Addition of ethyl (2-amino-4-methylthiazole)-5-carboxylate to the appropriate phenyl isocyanates, as outlined in **EXAMPLE 1**, was also used to synthesise **EXAMPLES 2** to **5** listed in **TABLE 1** below.

TABLE 1

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
2		2-[3-(3-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester	3.94	324.1 $[M+H]^+$
3		2-[3-(4-Ethoxycarbonyl phenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester	3.88	378.1 $[M+H]^+$
4		4-Methyl-2-[3-(4-methyl sulfanylphenyl)ureido]thiazole-5-carboxylic acid ethyl ester	3.95	352.1 $[M+H]^+$
5		4-Methyl-2-[3-phenyl ureido]thiazole-5-carboxylic acid ethyl ester	3.79	306.1 $[M+H]^+$

EXAMPLE 6

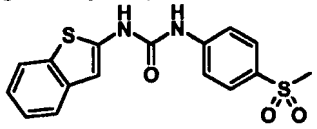
1-(4-Acetylphenyl)-3-benzo[b]thiophen-2-ylurea



To a solution of benzothiophene-2-carbonyl chloride (0.64 g, 3.26 mmol) in THF (10 mL) at 0°C was added a solution of sodium azide (0.25 g, 3.85 mmol) in water (2 mL) over 10 min dropwise. The reaction mixture was extracted with Et_2O (20 mL), CH_2Cl_2 (2 x 20 mL) and EtOAc (2 x 10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under vacuum to give a solid, which was taken up in toluene (30 mL) and refluxed under argon for 90 min. The mixture was cooled to 20°C, 4-aminoacetophenone (0.44 g, 3.25 mmol) was added and the reaction was stirred for 18h. The precipitate was collected by filtration and purified by flash chromatography (SiO_2, eluting with 5:95, 10:90 then 20:80 EtOAc, CH_2Cl_2) to give the title compound: RT = 3.73 min; *m/z* (ES^+) = 311.1 $[M + H]^+$.

EXAMPLE 7

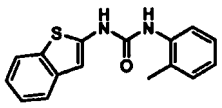
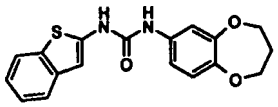
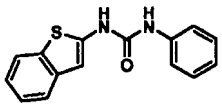
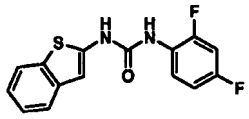
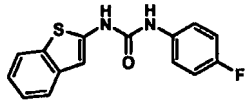
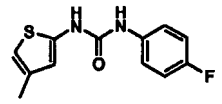
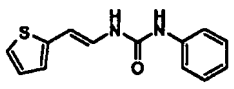
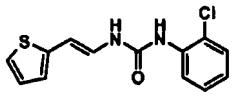
1-Benzo[b]thiophen-2-yl-3-(4-methanesulfonylphenyl)urea



The Curtius rearrangement to give benzothiophene-2-isocyanate followed by addition of the appropriate aniline, as outlined in **EXAMPLE 6**, was used to synthesise the title compound: RT = 3.55 min; *m/z* (ES^+) = 347.1 $[M + H]^+$.

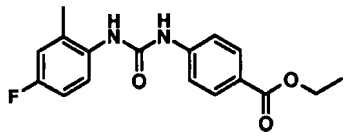
The compounds in **TABLE 2** are commercially available, however they can be prepared from the appropriate acid chlorides and anilines using the method outlined in **EXAMPLE 6.**

TABLE 2

Ex	Structure	Name	Source	RT (min)	*m/z* (ES^+)
8		1-Benzo[b] thiophen-2-yl-3-(2-methyl phenyl)urea	Maybridge	3.84	283.0 $[M+H]^+$
9		1-Benzo[b] thiophen-2-yl-3-(3,4-dihydro-2H-benzo[b] [1,4]dioxepin-7-yl)urea	Maybridge	4.02	340.9 $[M+H]^+$
10		1-Benzo[b] thiophen-2-yl-3-phenylurea	Maybridge	3.89	269.0 $[M+H]^+$
11		1-Benzo[b] thiophen-2-yl-3-(2,4-difluoro phenyl)urea	Maybridge	3.97	304.9 $[M+H]^+$
12		1-Benzo[b] thiophen-2-yl-3-(4-fluoro phenyl)urea	Maybridge	3.87	287.0 $[M+H]^+$
13		1-(4-Fluoro phenyl)-3-(4-methylthiophen-2-yl)urea	Maybridge	3.62	251.0 $[M+H]^+$
14		1-Phenyl-3-(2-thiophen-2-yl vinyl)urea	Maybridge	3.62	245.1 $[M+H]^+$
15		1-(2-Chloro phenyl)-3-(2-thiophen-2-yl vinyl)urea	Maybridge	3.92	278.9 $[M+H]^+$

EXAMPLE 16

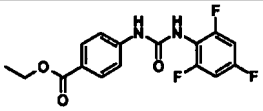
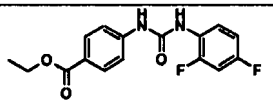
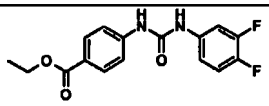
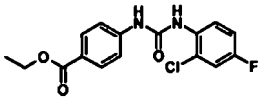
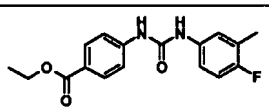
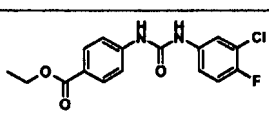
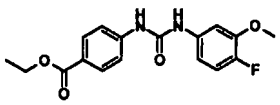
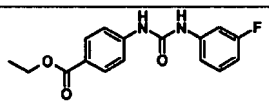
4-[3-(4-Fluoro-2-methylphenyl)ureido]benzoic acid ethyl ester

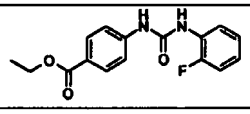


To a solution of 4-fluoro-2-methylaniline (34 mg, 0.27 mmol) in toluene (0.5 mL) was added ethyl 4-isocyanatobenzoate (50 mg, 0.26 mmol) in toluene (0.5 mL). The reaction mixture was stirred for 18h and the resulting precipitate was collected by filtration to give the title compound: RT = 3.70 min; *m/z* (ES^+) = 317.3 $[M + H]^+$.

Addition of the appropriate anilines to ethyl 4-isocyanatobenzoate, as outlined in **EXAMPLE 16**, was also used to synthesise **EXAMPLES 17** to **25** listed in **TABLE 3** below.

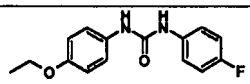
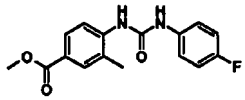
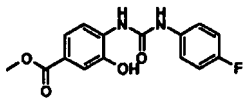
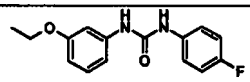
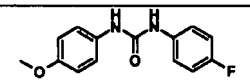
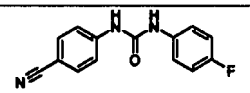
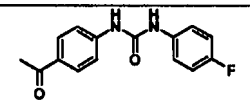
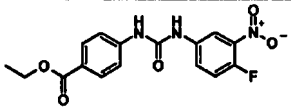
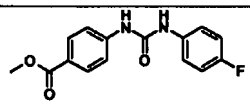
TABLE 3

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
17		4-[3-(2,4,6-Trifluorophenyl) ureido]benzoic acid ethyl ester	3.56	339.2 $[M+H]^+$
18		4-[3-(2,4-Difluorophenyl) ureido]benzoic acid ethyl ester	3.65	321.2 $[M+H]^+$
19		4-[3-(3,4-Difluorophenyl) ureido]benzoic acid ethyl ester	3.99	321.2 $[M+H]^+$
20		4-[3-(2-Chloro-4-fluoro phenyl)ureido]benzoic acid ethyl ester	3.89	337.2 $[M+H]^+$
21		4-[3-(4-Fluoro-3-methyl phenyl)ureido]benzoic acid ethyl ester	3.79	317.3 $[M+H]^+$
22		4-[3-(3-Chloro-4-fluoro phenyl)ureido]benzoic acid ethyl ester	3.82	337.2 $[M+H]^+$
23		4-[3-(4-Fluoro-3-methoxy phenyl)ureido]benzoic acid ethyl ester	3.84	333.3 $[M+H]^+$
24		4-[3-(3-Fluorophenyl)ureido] benzoic acid ethyl ester	3.76	303.2 $[M+H]^+$

25		4-[3-(2-Fluorophenyl)ureido] benzoic acid ethyl ester	3.62	303.2 $[M+H]^+$

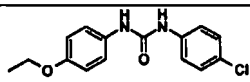
Addition of appropriate amines to 4-fluorophenyl isocyanate, as outlined in **EXAMPLE 16**, was also used to synthesise **EXAMPLES 26** to **34** listed in **TABLE 4** below.

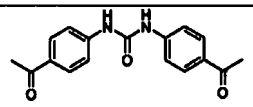
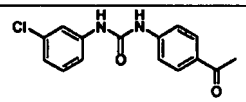
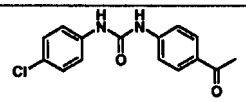
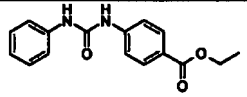
TABLE 4

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
26		1-(4-Ethoxyphenyl)-3-(4-fluorophenyl)urea	3.56	275.2 $[M+H]^+$
27		4-[3-(4-Fluorophenyl)ureido]-3-methylbenzoic acid methyl ester	3.66	303.2 $[M+H]^+$
28		4-[3-(4-Fluorophenyl)ureido]-3-hydroxybenzoic acid methyl ester	3.65	305.2 $[M+H]^+$
29		1-(3-Ethoxyphenyl)-3-(4-fluorophenyl)urea	3.60	275.2 $[M+H]^+$
30		1-(4-Fluorophenyl)-3-(4-methoxyphenyl)urea	3.50	261.2 $[M+H]^+$
31		1-(4-Cyanophenyl)-3-(4-fluorophenyl)urea	3.60	256.2 $[M+H]^+$
32		1-(4-Acetylphenyl)-3-(4-fluorophenyl)urea	3.33	273.2 $[M+H]^+$
33		4-[3-(4-Fluoro-3-nitrophenyl)ureido]benzoic acid ethyl ester	3.77	348.2 $[M+H]^+$
34		4-[3-(4-Fluorophenyl)ureido] benzoic acid methyl ester	3.52	289.2 $[M+H]^+$

Addition of appropriate amines to the appropriate phenyl isocyanate, as outlined in **EXAMPLE 16**, was also used to synthesise **EXAMPLES 35** to **39** listed in **TABLE 5** below.

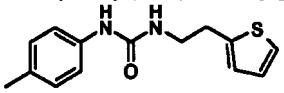
TABLE 5

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
35		1-(4-Chlorophenyl)-3-(4-ethoxyphenyl)urea	3.77	291.1 $[M+H]^+$

36		1,3-Bis(4-acetylphenyl)urea	3.29	297.1 $[M+H]^+$
37		1-(4-Acetylphenyl)-3-(3-chlorophenyl)urea	3.59	289.1 $[M+H]^+$
38		1-(4-Acetylphenyl)-3-(4-chlorophenyl)urea	3.60	577.3 $[2M+H]^+$
39		4-(3-Phenylureido)benzoic acid ethyl ester	3.66	285.2 $[M+H]^+$

EXAMPLE 40

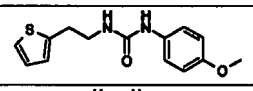
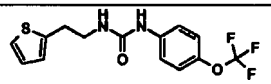
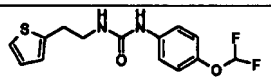
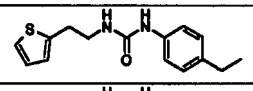
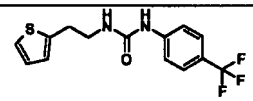
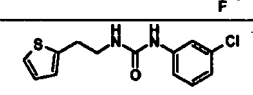
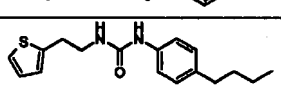
1-(2-Thiophen-2-ylethyl)-3-(4-methylphenyl) urea

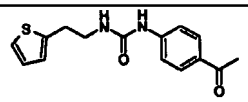
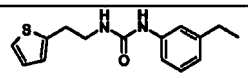
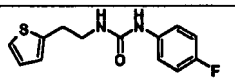
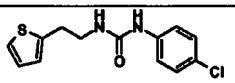
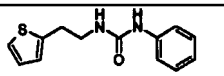
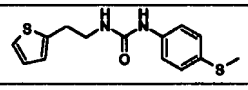


A solution of 2-thiophen-2-ylethylamine (30 mg, 0.24 mmol) in toluene (3 mL) was added to *p*-tolyl isocyanate (47 mg, 0.35 mmol) and shaken for 18h. The resulting precipitate was filtered and washed with toluene to give the title compound: RT = 3.70 min; *m/z* (ES^+) = 261.0 $[M + H]^+$.

Addition of 2-thiophen-2-ylethylamine to the appropriate isocyanates, as outlined in **EXAMPLE 40**, was also used to synthesise **EXAMPLES 41** to **53** listed in **TABLE 6** below.

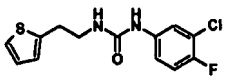
TABLE 6

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
41		1-(4-Methoxyphenyl)-3-(2-thiophen-2-ylethyl)urea	3.40	277.0 $[M+H]^+$
42		1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethoxyphenyl)urea	3.85	331.1 $[M+H]^+$
43		1-(4-Difluoromethoxy-phenyl)-3-(2-thiophen-2-ylethyl)urea	3.96	313.0 $[M+H]^+$
44		1-(4-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea	3.75	275.1 $[M+H]^+$
45		1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethylphenyl)urea	3.83	315.1 $[M+H]^+$
46		1-(3-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea	3.83	281.1 $[M+H]^+$
47		1-(4-Butylphenyl)-3-(2-thiophen-2-ylethyl)urea	4.06	303.1 $[M+H]^+$

48		1-(4-Acetylphenyl)-3-(2-thiophen-2-ylethyl)urea	3.38	289.1 $[M+H]^+$
49		1-(3-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea	3.83	275.1 $[M+H]^+$
50		1-(4-Fluorophenyl)-3-(2-thiophen-2-ylethyl)urea	3.57	265.1 $[M+H]^+$
51		1-(4-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea	3.71	281.1 $[M+H]^+$
52		1-Phenyl-3-(2-thiophen-2-yl ethyl)urea	3.50	247.1 $[M+H]^+$
53		1-(4-Methylsulfanylphenyl)-3-(2-thiophen-2-ylethyl)urea	3.70	293.1 $[M+H]^+$

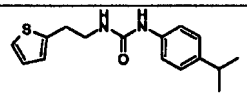
EXAMPLE 54 in **TABLE 7** is commercially available, however it can be prepared using the method outlined in **EXAMPLE 40.**

TABLE 7

Ex	Structure	Name	Source	RT (min)	*m/z* (ES^+)
54		1-(3-Chloro-4-fluoro-phenyl)-3-(2-thiophen-2-ylethyl)urea	Tripos	3.63	299.0 $[M+H]^+$

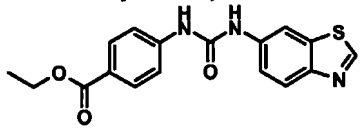
EXAMPLE 55 in **TABLE 8** can be prepared from the addition of 2-thiophen-2-ylethylamine to the appropriate isocyanate using the method outlined in **EXAMPLE 40.**

TABLE 8

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
55		1-(4-Isopropylphenyl)-3-(2-thiophen-2-ylethyl)-urea	3.78	$[M+H]^+$

EXAMPLE 56

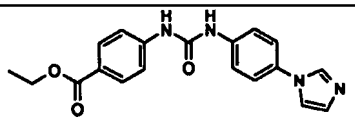
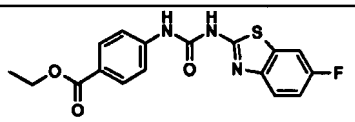
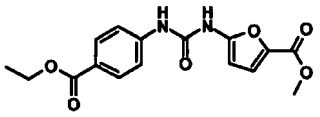
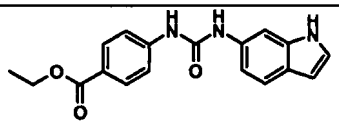
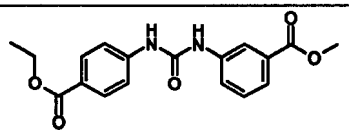
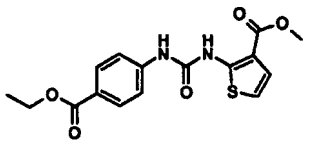
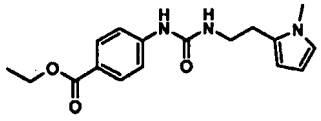
4-(3-Benzothiazol-6-ylureido)benzoic acid ethyl ester

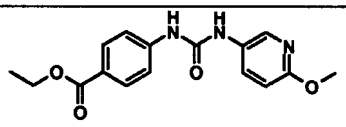
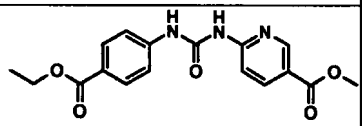
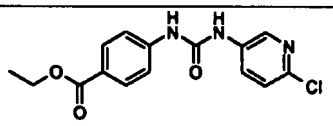
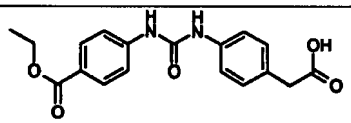
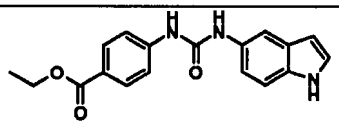
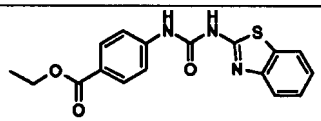
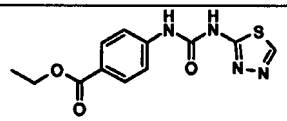
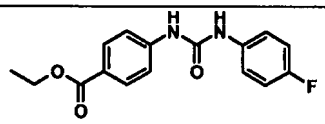
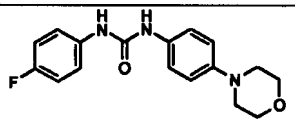
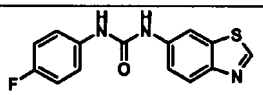
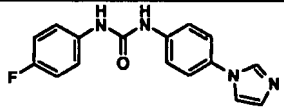
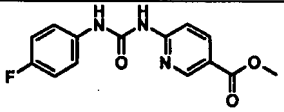


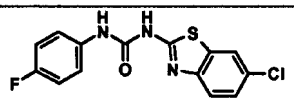
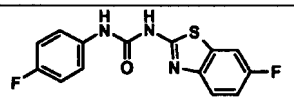
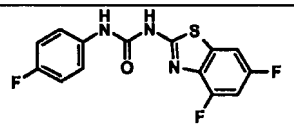
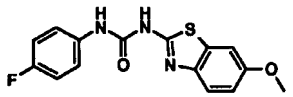
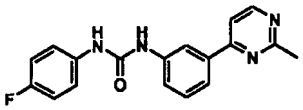
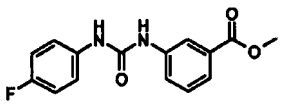
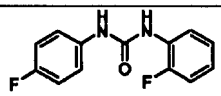
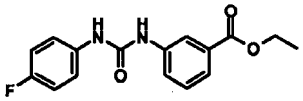
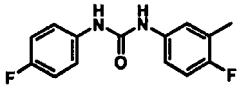
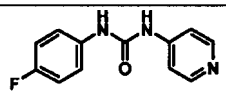
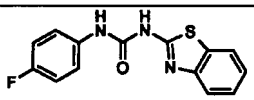
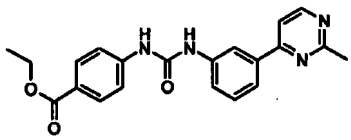
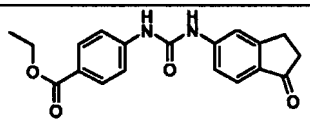
A solution of ethyl 4-isocyanatobenzoate (29 mg, 0.15 mmol) in DMF (1.7 mL) was added to 6-aminobenzothiazole (30 mg, 0.20 mmol) and shaken for 18h. MP-isocyanate (360 mg, 0.58 mmol, 4.58 mmol/g, 3.9 eq) was added to the mixture and shaken for 20h. The resin was removed by filtration and the solvent was removed under vacuum to give the title compound: RT = 3.71 min; *m/z* (ES^+) = 341.9 $[M + H]^+$.

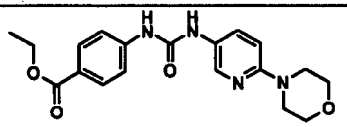
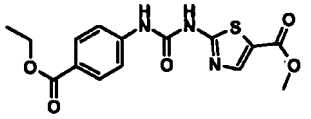
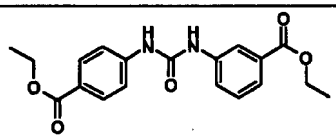
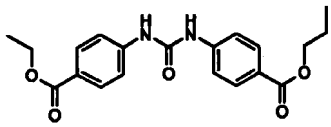
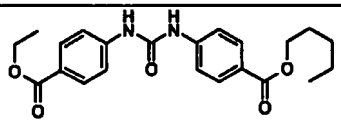
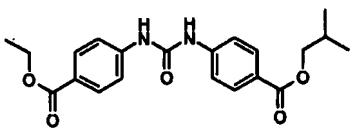
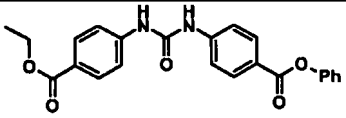
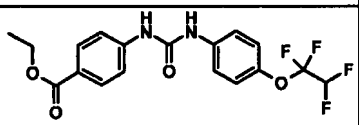
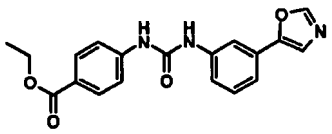
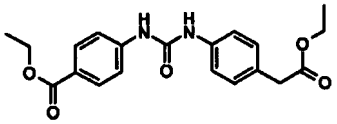
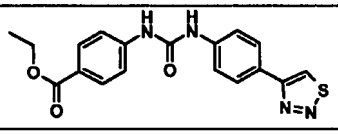
Addition of the appropriate amines to ethyl 4-isocyanatobenzoate or 4-fluorophenyl isocyanate, as outlined in **EXAMPLE 56**, was also used to synthesise **EXAMPLES 57** to **130** listed in **TABLE 9** below.

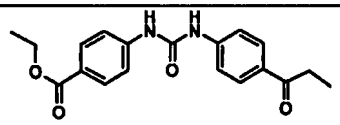
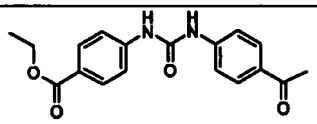
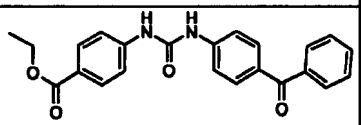
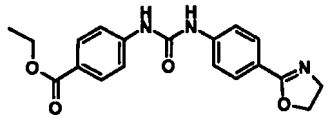
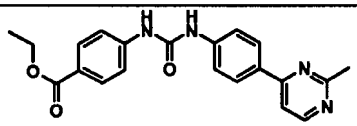
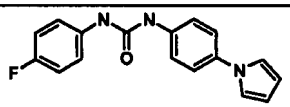
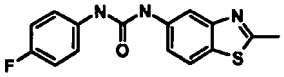
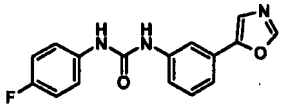
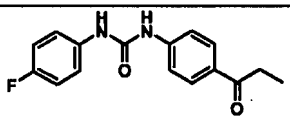
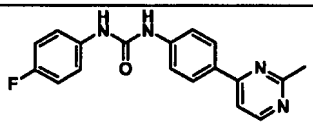
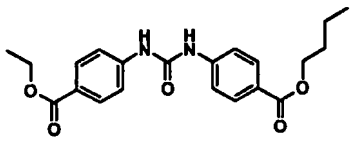
TABLE 9

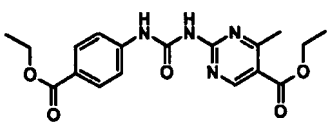
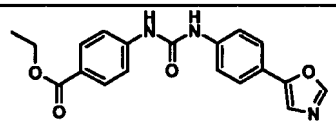
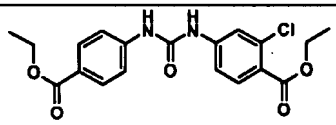
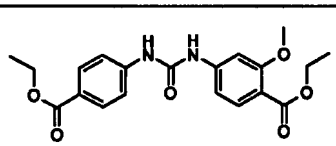
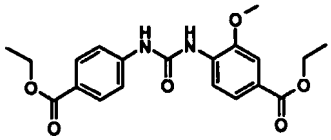
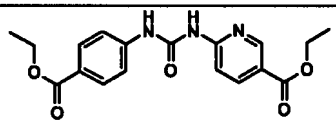
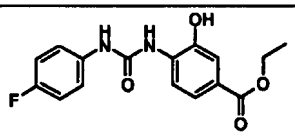
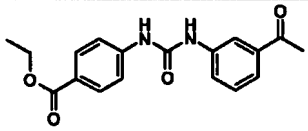
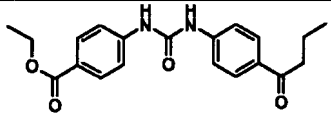
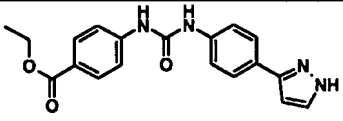
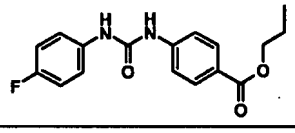
Ex	Structure	Name	RT (min)	*m/z* (ES^+)
57		4-[3-(4-Imidazol-1-yl phenyl)ureido]benzoic acid ethyl ester	2.90	351.2 $[M+H]^+$
58		4-[3-(6-Fluorobenzo thiazol-2-yl)ureido] benzoic acid ethyl ester	3.95	359.9 $[M+H]^+$
59		5-[3-(4-Ethoxycarbonyl phenyl)ureido]furan-2-carboxylic acid methyl ester	3.72	333.0 $[M+H]^+$
60		4-[3-(1H-Indol-6-yl) ureido]benzoic acid ethyl ester	3.74	324.3 $[M+H]^+$
61		4-[3-(3-Methoxycarbonyl phenyl)ureido]benzoic acid ethyl ester	3.68	343.3 $[M+H]^+$
62		2-[3-(4-Ethoxycarbonyl phenyl)ureido]thiophene-3-carboxylic acid methyl ester	4.05	348.9 $[M+H]^+$
63		4-{3-[2-(1-Methyl-1H-pyrrol-2-yl)ethyl] ureido}benzoic acid ethyl ester	3.64	316.3 $[M+H]^+$

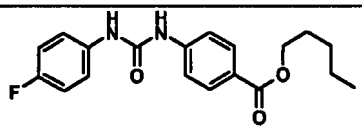
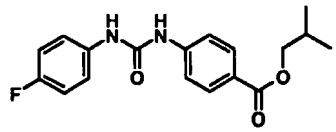
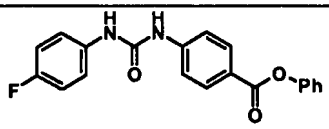
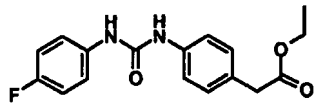
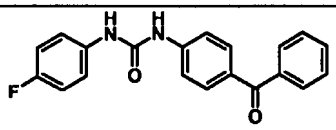
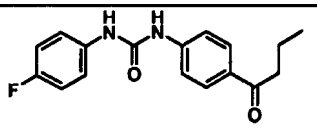
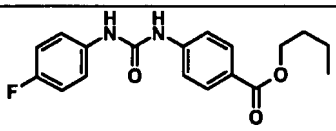
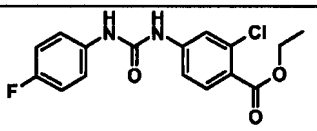
64		4-[3-(6-Methoxypyridin-3-yl)ureido]benzoic acid ethyl ester	3.44	316.3 $[M+H]^+$
65		6-[3-(4-Ethoxycarbonyl phenyl)ureido]nicotinic acid methyl ester	4.06	344.0 $[M+H]^+$
66		4-[3-(6-Chloropyridin-3-yl)ureido]benzoic acid ethyl ester	3.40	320.2 $[M+H]^+$
67		4-[3-(4-Carboxymethyl phenyl)ureido]benzoic acid ethyl ester	3.15	343.3 $[M+H]^+$
68		4-[3-(1H-Indol-5-yl) ureido]benzoic acid ethyl ester	3.69	324.3 $[M+H]^+$
69		4-(3-Benzothiazol-2-ylureido)benzoic acid ethyl ester	3.94	341.9 $[M+H]^+$
70		4-(3-[1,3,4]Thiadiazol-2-ylureido)benzoic acid ethyl ester	3.19	293.2 $[M+H]^+$
71		4-[3-(4-Fluorophenyl) ureido]benzoic acid ethyl ester	3.67	303.3 $[M+H]^+$
72		1-(4-Fluorophenyl)-3-(4-morpholin-4-ylphenyl)urea	3.00	316.3 $[M+H]^+$
73		1-Benzothiazol-6-yl-3-(4-fluorophenyl)urea	3.48	288.2 $[M+H]^+$
74		1-(4-Fluorophenyl)-3-(4-imidazol-1-ylphenyl)urea	2.61	296.9 $[M+H]^+$
75		6-[3-(4-Fluorophenyl) ureido]nicotinic acid methyl ester	3.50	290.2 $[M+H]^+$

76		1-(6-Chlorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea	4.12	322.2 $[M+H]^+$
77		1-(6-Fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea	4.07	305.9 $[M+H]^+$
78		1-(4,6-Difluorobenzo thiazol-2-yl)-3-(4-fluorophenyl)urea	3.94	323.9 $[M+H]^+$
79		1-(4-Fluorophenyl)-3-(6-methoxybenzothiazol-2-yl)urea	3.59	318.2 $[M+H]^+$
80		1-(4-Fluorophenyl)-3-[3-(2-methylpyrimidin-4-yl) phenyl]urea	3.32	323.2 $[M+H]^+$
81		3-[3-(4-Fluorophenyl) ureido]benzoic acid methyl ester	3.50	289.3 $[M+H]^+$
82		1-(4-Fluorophenyl)-3-(2-fluorophenyl)urea	3.52	249.2 $[M+H]^+$
83		3-[3-(4-Fluorophenyl) ureido]benzoic acid ethyl ester	3.54	303.3 $[M+H]^+$
84		1-(4-Fluoro-3-methyl phenyl)-3-(4-fluoro phenyl)urea	3.61	263.2 $[M+H]^+$
85		1-(4-Fluorophenyl)-3-pyridin-4-ylurea	2.31	232.2 $[M+H]^+$
86		1-Benzothiazol-2-yl-3-(4-fluorophenyl)urea	3.61	288.2 $[M+H]^+$
87		4-{3-[3-(2-Methyl pyrimidin-4-yl)phenyl] ureido}benzoic acid ethyl ester	3.64	377.1 $[M+H]^+$
88		4-[3-(1-Oxoindan-5-yl) ureido]benzoic acid ethyl ester	3.56	339.1 $[M+H]^+$

89		4-[3-(6-Morpholin-4-yl-pyridin-3-yl)ureido] benzoic acid ethyl ester	2.84	371.1 $[M+H]^+$
90		2-[3-(4-Ethoxycarbonyl phenyl)ureido]thiazole-5-carboxylic acid methyl ester	3.81	350.1 $[M+H]^+$
91		4-[3-(3-Ethoxycarbonyl phenyl)ureido]benzoic acid ethyl ester	3.94	357.1 $[M+H]^+$
92		4-[3-(4-Ethoxycarbonyl phenyl)ureido]benzoic acid propyl ester	4.07	371.1 $[M+H]^+$
93		4-[3-(4-Ethoxycarbonyl phenyl)ureido]benzoic acid pentyl ester	4.57	399.1 $[M+H]^+$
94		4-[3-(4-Ethoxycarbonyl phenyl)ureido]benzoic acid isobutyl ester	4.14	385.1 $[M+H]^+$
95		4-[3-(4-Ethoxycarbonyl phenyl)ureido]benzoic acid phenyl ester	4.09	405.1 $[M+H]^+$
96		4-{3-[4-(1,1,2,2-Tetra fluoroethoxy)phenyl] ureido}benzoic acid ethyl ester	3.94	401.0 $[M+H]^+$
97		4-[3-(3-Oxazol-5-yl phenyl)ureido]benzoic acid ethyl ester	3.90	352.1 $[M+H]^+$
98		4-[3-(4-Ethoxycarbonyl methylphenyl)ureido] benzoic acid ethyl ester	3.81	371.1 $[M+H]^+$
99		4-[3-(4-[1,2,3]Thiadiazol-4-ylphenyl)ureido] benzoic acid ethyl ester	3.79	369.0 $[M+H]^+$

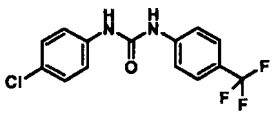
100		4-[3-(4-Propionylphenyl) ureido]benzoic acid ethyl ester	3.74	341.1 $[M+H]^+$
101		4-[3-(4-Acetylphenyl) ureido]benzoic acid ethyl ester	3.77	327.1 $[M+H]^+$
102		4-[3-(4-Benzoylphenyl) ureido]benzoic acid ethyl ester	3.99	389.1 $[M+H]^+$
103		4-{3-[4-(4,5-Dihydro oxazol-2-yl)phenyl] ureido}benzoic acid ethyl ester	2.87	354.0 $[M+H]^+$
104		4-{3-[4-(2-Methyl pyrimidin-4-yl)phenyl] ureido}benzoic acid ethyl ester	3.61	377.0 $[M+H]^+$
105		1-(4-Fluorophenyl)-3-(4-pyrrol-1-ylphenyl)urea	4.01	296.1 $[M+H]^+$
106		1-(4-Fluorophenyl)-3-(2-methylbenzothiazol-5-yl)urea	3.45	302.0 $[M+H]^+$
107		1-(4-Fluorophenyl)-3-(3-oxazol-5-ylphenyl)urea	3.56	298.1 $[M+H]^+$
108		1-(4-Fluorophenyl)-3-(4-propionylphenyl)urea	3.81	287.1 $[M+H]^+$
109		1-(4-Fluorophenyl)-3-[4-(2-methylpyrimidin-4-yl)phenyl]urea	3.39	323.0 $[M+H]^+$
110		4-[3-(4-Ethoxycarbonyl phenyl)ureido]benzoic acid butyl ester	4.16	385.1 $[M+H]^+$

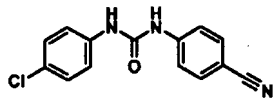
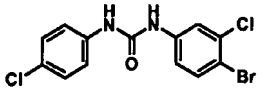
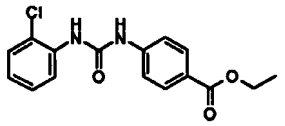
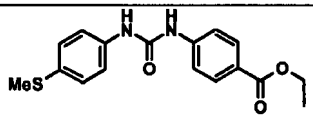
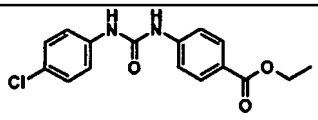
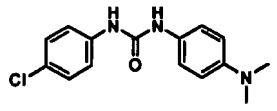
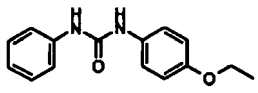
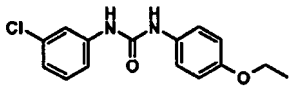
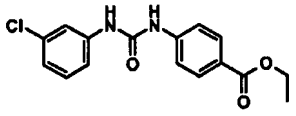
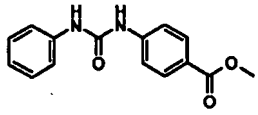
111		2-[3-(4-Ethoxycarbonyl phenyl)ureido]-4-methyl pyrimidine-5-carboxylic acid ethyl ester	3.87	373.1 $[M+H]^+$
112		4-[3-(4-Oxazol-5-yl phenyl)ureido]benzoic acid ethyl ester	3.90	352.1 $[M+H]^+$
113		2-Chloro-4-[3-(4-ethoxy carbonylphenyl)ureido] benzoic acid ethyl ester	4.04	391.1 $[M+H]^+$
114		4-[3-(4-Ethoxycarbonyl phenyl)ureido]-2-methoxybenzoic acid ethyl ester	3.74	387.1 $[M+H]^+$
115		4-[3-(4-Ethoxycarbonyl phenyl)ureido]-3-methoxybenzoic acid ethyl ester	4.04	387.1 $[M+H]^+$
116		6-[3-(4-Ethoxycarbonyl phenyl)ureido]nicotinic acid ethyl ester	4.09	358.1 $[M+H]^+$
117		4-[3-(4-Fluorophenyl) ureido]-3-hydroxy benzoic acid ethyl ester	3.69	319.1 $[M+H]^+$
118		4-[3-(3-Acetylphenyl) ureido]benzoic acid ethyl ester	3.70	327.0 $[M+H]^+$
119		4-[3-(4-Butyrylphenyl) ureido]benzoic acid ethyl ester	4.20	355.0 $[M+H]^+$
120		4-{3-[4-(1H-Pyrazol-3-yl)phenyl]ureido}benzoic acid ethyl ester	3.74	351.0 $[M+H]^+$
121		4-[3-(4-Fluorophenyl) ureido]benzoic acid propyl ester	4.05	317.0 $[M+H]^+$

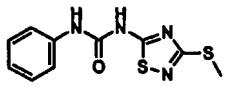
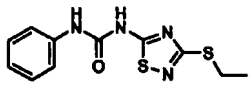
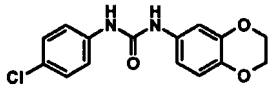
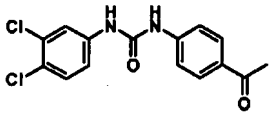
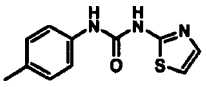
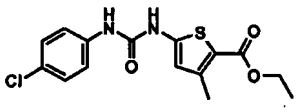
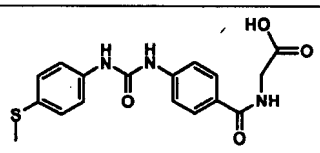
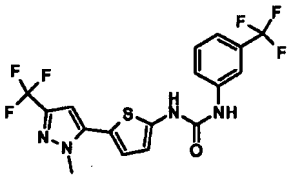
122		4-[3-(4-Fluorophenyl) ureido]benzoic acid pentyl ester	4.49	345.0 $[M+H]^+$
123		4-[3-(4-Fluorophenyl) ureido]benzoic acid isobutyl ester	4.20	331.0 $[M+H]^+$
124		4-[3-(4-Fluorophenyl) ureido]benzoic acid phenyl ester	4.17	351.0 $[M+H]^+$
125		{4-[3-(4-Fluorophenyl) ureido]phenyl}acetic acid ethyl ester	4.04	317.0 $[M+H]^+$
126		1-(4-Benzoylphenyl)-3-(4-fluorophenyl)urea	3.99	335.0 $[M+H]^+$
127		1-(4-Butyrylphenyl)-3-(4-fluorophenyl)urea	4.20	301.0 $[M+H]^+$
128		4-[3-(4-Fluorophenyl) ureido]benzoic acid butyl ester	4.20	331.0 $[M+H]^+$
129		2-Chloro-4-[3-(4-fluorophenyl)ureido] benzoic acid ethyl ester	4.09	336.9 $[M+H]^+$

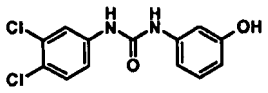
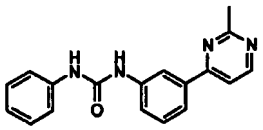
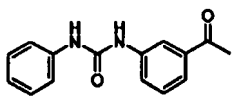
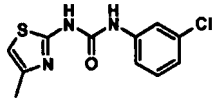
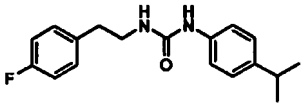
EXAMPLES 130 to **153** in **TABLE 10** are commercially available, however can be prepared using the method outlined in **EXAMPLE 56.**

TABLE 10

Ex	Structure	Name	Source	RT (min)	*m/z* (ES^+)
130		1-(4-Chloro phenyl)-3-(4-trifluoromethyl phenyl)urea	Tim Tec	4.14	314.9 $[M+H]^+$

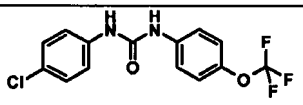
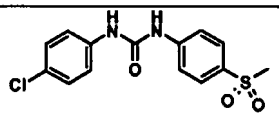
131		1-(4-Chloro phenyl)-3-(4-cyanophenyl)urea	Chembridge	3.81	271.9 $[M+H]^+$
132		1-(4-Bromo-3-chlorophenyl)-3-(4-chlorophenyl) urea	Exploratory Library	4.26	360.8 $[M+H]^+$
133		4-[3-(2-Chloro phenyl)ureido] benzoic acid ethyl ester	SALOR	3.99	318.9 $[M+H]^+$
134		4-[3-(4-Methyl sulfanylphenyl) ureido]benzoic acid ethyl ester	SALOR	3.87	331.0 $[M+H]^+$
135		4-[3-(4-Chloro phenyl)ureido] benzoic acid ethyl ester	SALOR	3.85	639.3 $[2M+H]^+$
136		1-(4-Chloro phenyl)-3-(4-dimethylamino phenyl)urea	SALOR	2.81	289.9 $[M+H]^+$
137		1-Phenyl-3-(4-ethoxyphenyl) urea	SALOR	3.60	257.2 $[M+H]^+$
138		1-(3-Chloro phenyl)-3-(4-ethoxyphenyl) urea	Chembridge	3.73	291.2 $[M+H]^+$
139		4-[3-(3-Chloro phenyl)ureido] benzoic acid ethyl ester	ChemDiv	4.33	319.0 $[M+H]^+$
140		4-(3-Phenyl ureido)benzoic acid methyl ester	Tim Tec	3.48	271.2 $[M+H]^+$

141		1-(3-Methyl sulfanyl[1,2,4] thiadiazol-5-yl)-3-phenylurea	SPECS	3.59	266.9 $[M+H]^+$
142		1-(3-Ethyl sulfanyl[1,2,4] thiadiazol-5-yl)-3-phenylurea	SPECS	3.63	281.1 $[M+H]^+$
143		1-(4-Chloro phenyl)-3-(2,3-dihydrobenzo [1,4]dioxan-6-yl)urea	Chembridge	3.92	304.9 $[M+H]^+$
144		1-(4-Acetyl phenyl)-3-(3,4-dichlorophenyl) urea	Sigma	3.94	322.9 $[M+H]^+$
145		1-Thiazol-2-yl-3-(4-methylphenyl) urea	Chembridge	3.39	233.9 $[M+H]^+$
146		5-[3-(4-Chloro phenyl)ureido]-3-methylthiophene-2-carboxylic acid ethyl ester	Chembridge	3.94	338.9 $[M+H]^+$
147		{4-[3-(4-Methyl sulfanylphenyl) ureido]benzoyl amino}acetic acid	SALOR	3.42	360.0 $[M+H]^+$
148		1-[5-(2-Methyl-5-trifluoro methyl-2H -pyrazol-3-yl) thiophen-2-yl]-3-(3-trifluoro methylphenyl) urea	Maybridge	3.83	434.9 $[M+H]^+$

149		1-(3,4-Dichloro phenyl)-3-(3-hydroxyphenyl) urea	SALOR	3.58	297.1 $[M+H]^+$
150		1-[3-(2-Methyl pyrimidin-4-yl) phenyl]-3-phenylurea	Maybridge	3.42	304.9 $[M+H]^+$
151		1-(3-Acetyl phenyl)-3-phenylurea	SALOR	3.33	255.2 $[M+H]^+$
152		1-(3-Chloro phenyl)-3-(4-methylthiazol-2-yl)urea	Chembridge	3.63	268.1 $[M+H]^+$
153		1-[2-(4-Fluorophenyl) ethyl]-3-(4-isopropyl phenyl)urea	Chembridge	3.87	301.2 $[M+H]^+$

EXAMPLES 154 and **155** in **TABLE 11**, which have been previously reported, can be prepared from the appropriate aniline and isocyanate using the method outlined in **EXAMPLE 56**.

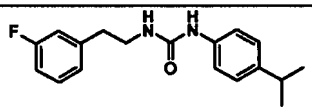
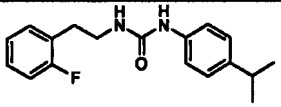
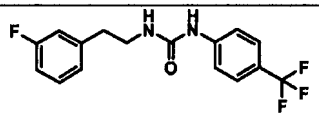
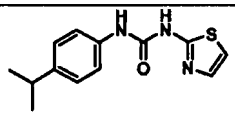
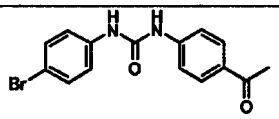
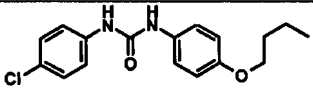
TABLE 11

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
154		1-(4-Chlorophenyl)-3-(4-trifluoromethoxyphenyl) urea	4.11	330.9 $[M+H]^+$
155		1-(4-Chlorophenyl)-3-(4-methanesulfonylphenyl) urea	3.77	324.9 $[M+H]^+$

EXAMPLES 156 to **161** in **TABLE 12** can be prepared from the appropriate aniline and isocyanate using the method outlined in **EXAMPLE 56**.

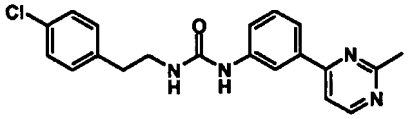
TABLE 12

Ex	Structure	Name	RT (min)	*m/z* (ES^+)

156		1-[2-(3-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea	3.87	301.2 $[M+H]^+$
157		1-[2-(2-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea	3.87	301.2 $[M+H]^+$
158		1-[2-(3-Fluorophenyl)ethyl]-3-(4-trifluoromethylphenyl) urea	3.83	327.2 $[M+H]^+$
159		1-(4-Isopropylphenyl)-3-thiazol-2-ylurea	3.62	262.2 $[M+H]^+$
160		1-(4-Acetylphenyl)-3-(4-bromophenyl)urea	3.97	332.9 $[M+H]^+$
161		1-(4-Butoxyphenyl)-3-(4-chlorophenyl)urea	4.39	319.0 $[M+H]^+$

EXAMPLE 162

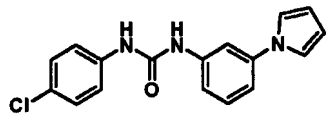
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea



To a solution of triphosgene (400 mg, 1.35 mmol) in CH_2Cl_2 (50 mL) at 0°C was added DIPEA (0.4 mL, 4.0 mmol) followed by 3-(2-methylpyrimidin-4-yl) phenylamine (740 mg, 4.0 mmol) in portions. After addition, the ice bath was removed, DIPEA (0.4 mL, 4.0 mmol) and 2-(4-chlorophenyl)ethylamine (622 mg, 4.0 mmol) were added. The reaction mixture was stirred for 18h. CH_2Cl_2 (50 mL) was added and the organics were washed with water (20 mL), 1M NaOH solution (20 mL) and brine (20 mL) before being dried ($MgSO_4$) and removing the solvent *in vacuo*. The resulting powder was recrystallised from methanol to give the title compound: δ_H(DMSO): 2.67 (3H, s), 2.76 (2H, t), 3.35 (2H, m), 6.12 (1H, m), 7.28 (2H, d), 7.36-7.40 (3H, m), 7.61 (1H, d), 7.67 (1H, d), 7.75 (1H, d), 8.19 (1H, s), 8.72-8.73 (2H, m); RT = 3.57 min; *m/z* (ES^+) = 367.19 $[M + H]^+$.

EXAMPLE 163

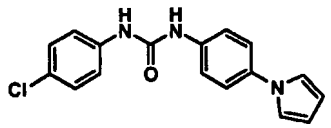
1-(4-Chlorophenyl)-3-(3-pyrrol-1-ylphenyl) urea



To a solution of 4-chlorophenylisocyanate (100 mg, 0.65 mmol) in CH_2Cl_2 (7 mL) was added 3-(1H-pyrrol-1-yl) aniline (103 mg, 0.65 mmol) at rt. The reaction mixture was stirred at rt for 4h and the resulting solid collected by filtration. Trituration with Et_2O, followed by filtration gave the title compound: δ_H (DMSO): 6.27 (2H, t), 7.15-7.18 (1H, m), 7.24-7.27 (3H, m), 7.32-7.38 (3H, m), 7.49-7.51 (2H, m), 7.71 (1H, t), 8.85 (1H, s), 8.89 (1H, s); RT = 4.02 min; *m/z* (ES^+) = 312.13 $[M + H]^+$.

EXAMPLE 164

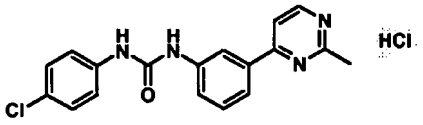
1-(4-Chlorophenyl)-3-(4-pyrrol-1-ylphenyl) urea



To a solution of 4-chlorophenylisocyanate (100 mg, 0.65 mmol) in CH_2Cl_2 (7 mL) was added 4-(1H-pyrrol-1-yl) aniline (103 mg, 0.65 mmol) at rt. The reaction mixture was stirred at rt for 16h and the resulting solid collected by filtration. Trituration with Et_2O, followed by filtration gave the title compound: δ_H (DMSO): 6.23 (2H, t), 7.27 (2H, t), 7.32-7.34 (2H, m), 7.46-7.54 (6H, m), 8.77 (1H, s), 8.82 (1H, s); RT = 4.01 min; *m/z* (ES^+) = 312.13 $[M + H]^+$.

EXAMPLE 165

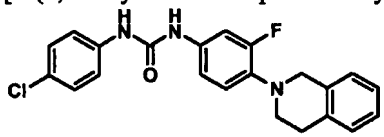
1-(4-Chlorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea hydrochloride



To a solution of 4-chlorophenylisocyanate (1.0 g, 6.5 mmol) in CH_2Cl_2 (20 mL) was added 3-(2-methylpyrimidin-4-yl)phenylamine (1.2 g, 6.5 mmol). The reaction mixture was stirred for 18h and the resulting precipitate collected by filtration to yield 2.05 g (93 %). The filtrate was dissolved in THF (10 mL) and 4M hydrogen chloride solution in dioxane (1.5 mL, 6.0 mmol) added. The resultant solid was filtered, dissolved in methanol and precipitated with Et_2O to yield, after filtration, the title compound: δ_H (CD_3OD): 2.96 (3H, s), 7.29 (2H, d), 7.47 (2H, d), 7.54-7.58 (1H, m), 7.68 (1H, d), 8.03 (1H, d), 8.36 (1H, d), 8.63 (1H, s), 8.96 (1H, d); RT = 3.45 min; *m/z* (ES^+) = 339.01 $[M + H]^+$.

EXAMPLE 166

1-(4-Chlorophenyl)-3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl] urea

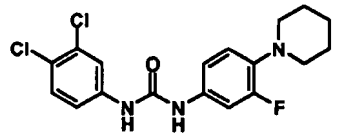


To a solution of 4-chlorophenylisocyanate (230 mg, 1.5 mmol) in CH_2Cl_2 (15 mL) was added 4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenylamine (363 mg, 1.5 mmol). The reaction

mixture was stirred for 18h and the resulting precipitate collected by filtration. Recrystallisation from MeOH gave the title compound: δ_H (DMSO): 2.91-2.94 (2H, m), 3.30-3.33 (2H, m), 4.18 (2H, s), 7.06-7.08 (2H, m), 7.18 (4H, s), 7.33-7.35 (2H, m), 7.48-7.50 (3H, m), 8.74 (1H, s), 8.81 (1H, s); RT = 4.20 min; *m/z* (ES^+) = 396.11 $[M + H]^+$.

EXAMPLE 167

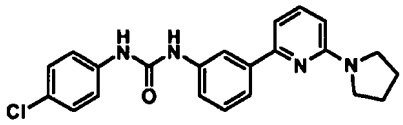
1-(3,4-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea



To a solution of 3,4-dichlorophenylisocyanate (282 mg, 1.50 mmol) in CH_2Cl_2 (7 mL) was added 3-fluoro-4-piperidin-1-yl-phenylamine (320 mg, 1.65 mmol). The reaction mixture was stirred for 18h and the resulting precipitate collected by filtration to give the title compound: δ_H (DMSO): 1.51-1.53 (2H, m), 1.61-1.67 (4H, m), 2.87-2.90 (4H, m), 6.94-6.98 (1H, m), 7.04-7.06 (1H, m), 7.30-7.33 (1H, m), 7.35-7.40 (1H, m), 7.50-7.52 (1H, d), 7.86 (1H, m), 8.76 (1H, s), 8.95 (1H, s); RT = 3.56 min; *m/z* (ES^+) = 381.98 $[M + H]^+$.

EXAMPLE 168

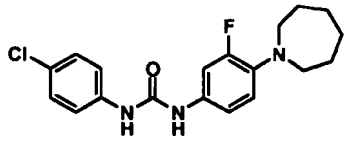
1-(4-Chlorophenyl)-3-[3-(6-pyrrolidin-1-ylpyridin-2-yl)phenyl] urea



A suspension of 2-(3-nitrophenyl)-6-pyrrolidin-1-ylpyridine (2.83 g, 10.52 mmol) and 10% palladium on carbon (0.50 g) in EtOH (50 mL) and CH_2Cl_2 (30 mL) was stirred under an atmosphere of hydrogen for 18h. The mixture was filtered through celite and the solvent removed under vacuum to give 3-(6-pyrrolidin-1-ylpyridin-2-yl) aniline, which was used without further purification. To a solution of 3-(6-pyrrolidin-1-ylpyridin-2-yl)aniline (1.01 g, 4.226 mmol) in CH_2Cl_2 (5 mL) was added 4-chlorophenyl isocyanate (0.59 g, 3.84 mmol). The reaction mixture was stirred for 18h and the resulting precipitate collected by filtration. The solid was purified by recrystallisation (MeOH/ CH_2Cl_2) to give the title compound: δ_H ($CDCl_3$): 1.97 (4H, m), 3.48 (4H, m), 6.42 (1H, d), 7.05 (1H, d), 7.33 (2H, d), 7.35 (1H, m), 7.50 (2H,d), 7.56 (2H, m), 7.63 (1H, d), 8.07 (1H, s), 8.78 (1H, s), 8.82 (1H, s); RT = 3.19 min; *m/z* (ES^+) = 393.13 $[M + H]^+$.

EXAMPLE 169

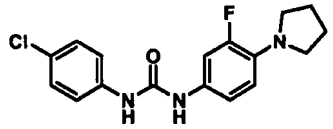
1-(4-Azepan-1-yl-3-fluorophenyl)-3-(4-chlorophenyl) urea



A mixture of 1-(2-fluoro-4-nitrophenyl)azepane (0.30 g, 1.26 mmol) and iron powder (0.22 g, 3.99 mmol) in saturated NH_4Cl (aq) (1.5 mL), THF (2 mL) and EtOH (4 mL) was heated at 80°C for 20h. The reaction was partitioned between CH_2Cl_2 and water, the organic phase was dried ($MgSO_4$) and the solvent removed to give 4-azepan-1-yl-3-fluorophenylamine. To a solution of 4-azepan-1-yl-3-fluorophenylamine (0.16 g, 0.779 mmol) in CH_2Cl_2 (2 mL) was added 4-chlorophenyl isocyanate (0.12 g, 0.779 mmol) and the reaction stirred for 18h. The resulting precipitate was collected by filtration to give the title compound: δ_H ($CDCl_3$): 1.56 (4H, m), 1.74 (4H, m), 3.24 (4H, m), 6.86 (1H, m), 6.96 (1H, m), 7.30 (2H, d), 7.35 (1H, m), 7.46 (2H, d), 8.55 (1H, s), 8.73 (1H, s); RT = 3.82 min; *m/z* (ES^+) = 362.06 $[M + H]^+$.

EXAMPLE 170

1-(4-Chlorophenyl)-3-(3-fluoro-4-pyrrolidin-1-ylphenyl) urea



A mixture of 1-(2-fluoro-4-nitrophenyl)pyrrolidine (0.26 g, 1.26 mmol) and iron powder (0.22 g, 3.99 mmol) in saturated NH_4Cl (aq) (1.5 mL), THF (2 mL) and EtOH (4 mL) was heated at 80°C for 20h. The reaction was partitioned between CH_2Cl_2 and water, the organic phase was dried ($MgSO_4$) and the solvent removed to give 3-fluoro-4-pyrrolidin-1-yl-phenylamine. To a solution of 3-fluoro-4-pyrrolidin-1-yl-phenylamine (0.13 g, 0.71 mmol) in CH_2Cl_2 (2 mL) was added 4-chlorophenylisocyanate (0.11 g, 0.71 mmol) and the reaction stirred for 18h. The resulting precipitate was collected by filtration to give the title compound: δ_H ($CDCl_3$): 1.88 (4H, m), 3.23 (4H, m), 6.69 (1H, m), 6.97 (1H, m), 7.30 (2H, d), 7.35 (1H, m), 7.46 (2H, d), 8.51 (1H, s), 8.71 (1H, s); RT = 3.44 min; *m/z* (ES^+) = 334.04 $[M + H]^+$.

The following compounds were also prepared by methods analogous to those described above:

EXAMPLE:

171 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethoxy)phenyl] urea
172 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-methoxyethoxy)phenyl] urea
173 1-(4-Chlorophenyl)-3-[3-(2-isopropylpyrimidin-4-yl)phenyl] urea
174 1-(4-Chlorophenyl)-3-(3-fluoro-4-[1,4]oxazepan-4-ylphenyl) urea
175 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
176 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
177 4-[3-(3-Fluoro-4-piperidin-1-ylphenyl)ureido]benzoic acid ethyl ester
178 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methoxyethoxy)phenyl] urea
179 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-morpholin-4-ylethoxy)phenyl] urea
180 1-(4-Chlorophenyl)-3-(4-pyridin-3-ylphenyl) urea
181 1-(4-Chlorophenyl)-3-[3-(6-methylpyrimidin-4-yl)phenyl] urea
182 1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-hydroxypiperidin-1-yl)phenyl] urea

183 1-(4-Chlorophenyl)-3-(4-pyridin-2-yl-phenyl) urea
184 1-(4-Chlorophenyl)-3-(4-pyridin-4-ylphenyl) urea
185 1-(4-Chlorophenyl)-3-[3-(2-piperidin-1-ylpyrimidin-4-yl)phenyl] urea
186 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethyl)phenyl] urea
187 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
188 1-(2,3-Dihydrobenzofuran-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
189 1-(3,5-Dimethoxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
190 1-(4-Chlorophenyl)-3-(3-pyrazol-1-ylphenyl) urea
191 1-(4-Chlorophenyl)-3-[3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)phenyl] urea
192 1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
193 1-(4-Morpholin-4-ylmethylphenyl)-3-(3-pyrrol-1-ylphenyl) urea
194 1-(4-Chlorophenyl)-3-[4-(4,4-difluoropiperidin-1-yl)-3-fluorophenyl] urea
195 1-(4-Butyrylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
196 1-(1-Methyl-1H-indazol-5-yl)-3-(4-morpholin-4-ylmethylphenyl) urea
197 1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrazol-1-ylphenyl) urea
198 1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
199 1-(3,5-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
200 1-(3-Chloro-4-fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
201 1-(4-Ethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
202 1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methyl-2H-pyrazol-3-yl)phenyl] urea
203 1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl] urea
204 1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-methylpiperidin-1-yl)phenyl] urea
205 1-Benzo[1,3]dioxol-5-yl-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
206 1-(4-Chlorophenyl)-3-[3-fluoro-4-(2-methylpiperidin-1-yl)phenyl] urea
207 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-methoxyphenyl) urea
208 1-(4-Chloro-2-hydroxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
209 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
210 1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-trifluoromethylpiperidin-1-yl)phenyl] urea
211 1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-methylpiperidin-1-yl)phenyl] urea
212 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-phenoxyphenyl) urea
213 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-phenoxyphenyl) urea
214 1-(4-Fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
215 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-methoxyphenyl) urea
216 1-(4-Cyanophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
217 1-(4-Chlorophenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
218 1-(4-Chloro-3-trifluoromethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
219 1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-trifluoromethylphenyl) urea
220 1-(3-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
221 1-(4-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
222 1-(4-Chlorophenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
223 1-(4-Chlorophenyl)-3-(3-dimethylaminophenyl) urea
224 1-(4-Chlorophenyl)-3-(3-fluoro-4-morpholin-4-ylphenyl) urea

225 1-[2-(4-Chlorophenyl)ethyl]-3-(3-pyrrol-1-ylphenyl) urea
226 1-(3,5-Dichlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
227 1-(3-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
228 1-(3,5-Bis-trifluoromethylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
229 1-(4-Acetylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
230 1-(4-Acetylphenyl)-3-[3-(6-methoxypyridin-2-yl)phenyl] urea
231 1-(4-Acetylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
232 1-(4-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
233 1-(3-Chloro-4-morpholin-4-ylphenyl)-3-(4-chlorophenyl) urea
234 1-(4-Chlorophenyl)-3-(4-piperidin-1-ylphenyl) urea
235 1-(4-Acetylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
236 1-(4-Butyrylphenyl)-3-(4-piperidin-1-ylphenyl) urea
237 1-[2-(4-Chlorophenyl)ethyl]-3-(4-morpholin-4-ylmethylphenyl) urea
238 1-(4-Chlorophenyl)-3-(1-methyl-1H-indazol-5-yl) urea
239 1-(3-Acetylphenyl)-3-[2-(4-chlorophenyl)ethyl] urea
240 1-(4-Chlorophenyl)-3-[3-(2-pyrrolidin-1-ylpyrimidin-4-yl)phenyl] urea
241 1-(4-Chlorophenyl)-3-(4-pyrazol-1-ylphenyl) urea
242 1-[2-(4-Chlorophenyl)ethyl]-3-[4-(morpholine-4-carbonyl)phenyl] urea

The biological activity of the compounds of the invention may be tested in the following assay systems:

The Yeast GPCR Antagonism Assay:

Yeast cells harboring the CB1 receptor gene and a FUS1p-LacZ transcriptional reporter on plasmids are grown at 30°C in selective minimal media buffered by Pipes buffer to pH 6.8. Following overnight incubation, yeast cells are harvested by centrifugation at 1000g for 10min, then resuspended in fresh buffered media to a cell density of $A_{600} = 0.3$. To set up the assay, 80μL of cells are inoculated into a 96-well flat bottom black plate containing 10μL of a range of dilution of test compounds in 10%DMSO, 0.5%BSA solution. The range of compound concentrations used for the dose response curve is usually 1nM-10μM. After a 15min incubation period at 30°C, 10μL of CB1 agonist (methanandamide or CP 55,940) is added to a final concentration of 2μM or 0.1μM respectively. The assay plates are then incubated at 30°C for a further 4h. At the end of this period, β-galactosidase enzyme activity within the cells is assayed fluorometrically by the addition 83μM of the substrate 4-methylumbelliferyl-β-D-galactopyranoside (MUG) in a 20μL volume of buffer containing 25mM Pipes pH 7.2 and 0.41% Triton X-100. The reaction is allowed to proceed for 45min at 30°C before being stopped by the addition of 20μL of 1M Na_2CO_3. MUG's hydrolysis product, β-methylumbelliferone (7-hydroxy-4-methylcoumarin), is measured via its fluorescence emission at 460nM following excitation at 360nM. The IC_{50} for each compound is then calculated as the concentration of compound needed to reduce the fluorescence increase, due to the addition of agonist, by 50%.

Competitive GTPγS binding assay:

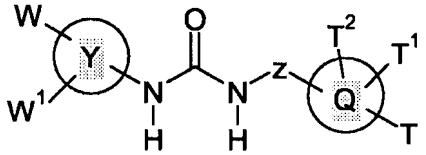
Membrane preparations of the human CB1 receptor expressed in HEK293 EBNA cells were purchased from PerkinElmer life sciences. Binding experiments were carried out in 96-round bottom plates in a total volume of 200μL of buffer A (20 mM Hepes, 3 mM $MgCl_2$, 100 mM NaCl, 1 mM EDTA, 0.1% BSA, pH 7.4) containing, in addition, 20μg of membrane, 0.1 nM [^{35}S] GTPγS (sp.act. 1250 Ci/mmole), 50 nM agonist CP-55940 (Tocris), 10 μM GDP and the required range of antagonist concentrations made up in DMSO to give a final DMSO concentration of 1%.

Following incubation for 1h at 30°C, the reactions were transferred to a 96-well GF/B MAFB filter plate (Millipore) pre-soaked in 20 mM Hepes, 3 mM $MgCl_2$, 100 mM NaCl and 1 mM EDTA, pH 7.4. The plate was then filtered and washed with 4 x 250 μL volumes of ice cold buffer A using a Multiscreen vacuum manifold (Millipore). After drying at 50°C for 2h, 30 μL of scintillant (Ultima Gold™, Packard) was added to each well and the plate counted for radioactivity in a Packard MicroBeta counter. Non-specific binding was determined by the addition of 30 μM GTPγS in place of antagonist. Basal [^{35}S] GTPγS binding determined in absence of agonist and antagonist and Maximal [^{35}S] GTPγS binding determined in presence of agonist but in absence of antagonist. IC_{50}'s were calculated from plots of % reduction in agonist stimulated [^{35}S] GTPγS binding versus $\log_{10}$ antagonist concentrations using the Xlfit3 program (idbs). IC_{50} being the concentration of antagonist required to reduce agonist stimulated [^{35}S] GTPγS binding by 50%.

The Examples of the present invention generally demonstrated efficacy in the above assays with IC_{50} results better than 10μM. It is advantageous that the IC_{50} be better than 5μM, even more advantageous if better than 1μM, and still more advantageous if better than 300nM.

CLAIMS:

1. A method of treating a condition associated with the CB-1 receptor by administering to a subject in need of such treatment a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

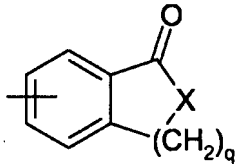
Y is phenyl, a 5- or 6-membered heteroaryl group, or a 9-membered bicyclic heteroaryl group attached to the urea through the 5-membered ring;

W is $COOR^1$, COR^1, C_{1-6}alkyl, C_{1-3}fluoroalkyl, C_{1-6}alkoxy, phenoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkoxy, C_{1-6}alkylthio, C_{3-6}cycloalkyl, chloro, fluoro, nitrile, $-(CH_2)_m-NR^2R^3$, $-O(CH_2)_n-NR^2R^3$, or 5- or 6-membered heteroaryl optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, C_{1-3}fluoroalkyl, C_{1-3}alkoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkyl, chloro, fluoro and $-(CH_2)_m-NR^2R^3$; or when Y is a 9-membered bicyclic heteroaryl group attached to the urea through the 5-membered ring, or when Z is C_{1-3}alkylene or C_{2-3}alkenylene, then W may be hydrogen;

W^1 is hydrogen, halogen, C_{1-3}alkyl, hydroxy or C_{1-3}alkoxy;

or W and W^1, when attached to adjacent carbon atoms on Y, together form a group $-O-(CH_2)_p-O-$, wherein p is 1, 2 or 3;

or the group formed from -Y, -(W) and $-(W^1)$ is:



wherein X is O or CH_2 and q is 1 or 2;

Z is C_{1-3}alkylene, C_{2-3}alkenylene or a bond;

Q is phenyl, or a 5- to 10-membered mono- or bicyclic heteroaryl group;

T is hydrogen, halogen, nitro, nitrile, $COOR^1$, COR^1, $-(CH_2)_m-NR^2R^3$, $CONHCH_2COOH$, C_{1-6}alkyl optionally substituted by $COOR^4$ or OR^4, C_{1-3}fluoroalkyl, C_{1-6}alkoxy, C_{1-3}fluoroalkoxy, C_{1-6}alkylthio, SOR^5, SO_2R^5; or a C_{3-6}cycloalkyl group, 5- to 7-membered heterocyclyl group or 5- to 10-membered heteroaryl group any one of which is optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, C_{1-3}fluoroalkyl, C_{1-3}alkoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkyl, chloro, fluoro, hydroxy and $-(CH_2)_m-NR^2R^3$;

T^1 and T^2 are independently selected from hydrogen, halogen, hydroxy, C_{1-3}alkyl and C_{1-3}alkoxy;

or T and T^1, when attached to adjacent carbon atoms on Q, together form a group

$-O-(CH_2)_p-O-$, wherein p is 1, 2 or 3;

m is 0, 1, 2 or 3;

n is 2 or 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or a 5- or 6-membered heteroaryl or heterocyclyl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl and C_{3-6}cycloalkyl, or R^2 and R^3 together with the nitrogen to which they are attached form a 5- to 7-membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and NR^4, and optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxyl;

R^4 is hydrogen or C_{1-3}alkyl; and

R^5 is C_{1-6}alkyl or C_{3-6}cycloalkyl.

2. The method according to claim 1 wherein when Y is phenyl.

3. The method according to claim 1 wherein when Y is a 5- or 6-membered heteroaryl group it is thienyl, thiazolyl or thiadiazolyl.

4. The method according to claim 1 wherein when Y is a 9-membered bicyclic heteroaryl group it is benzothienyl or benzothiazolyl.

5. The method according to claim 2 wherein W is $COOR^1$, COR^1, C_{1-6}alkoxy, C_{1-6}alkylthio, fluoro, chloro, C_{1-3}alkoxyC_{1-3}alkoxy, $-(CH_2)_m-NR^2R^3$, $-O(CH_2)_n-NR^2R^3$, or 5- or 6-membered heteroaryl optionally substituted by C_{1-3}alkyl.

6. The method according to any one of the preceding claims wherein W^1 is hydrogen.

7. The method according to any one of the preceding claims wherein Z is C_2alkylene, C_2alkenylene or a bond.

8. The method according to claim 7 wherein Z is a bond.

9. The method according to any one of the preceding claims wherein Q is phenyl.

10. The method according to any one of the preceding claims wherein T is halogen, $COOR^1$, COR^1, C_{1-6}alkyl, $-(CH_2)_m-NR^2R^3$ optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy, or a 5- to 10-membered heteroaryl group optionally substituted by C_{1-3}alkyl.

11. The method according to claim 10 wherein when T is $-(CH_2)_m-NR^2R^3$, m is 0 and R^2 and R^3 together with the nitrogen to which they are attached form a 5- to 7-membered heterocyclic ring.

12. The method according to any one of the preceding claims wherein T^1 and T^2 are hydrogen, halogen or hydroxy.

13. The method according to claim 12 wherein T^2 is hydrogen.

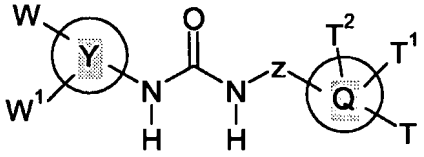
14. The method according to any one of the preceding claims wherein the substituents on the groups Y and Q are in the meta and/or para positions relative to the urea.

15. The method according to claim 1 wherein the compound of formula (I) is the compound of any one of Examples 1 to 242, or a pharmaceutically acceptable salt thereof.

16. The method according to any one of claims 1 to 14 for the treatment of obesity; psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, depression, cognitive disorders, memory disorders, obsessive compulsive disorders, anorexia, bulimia, attention disorders, epilepsy and related conditions affective and cognitive disorders brought about by disturbances in any of the central monoaminergic systems; a neurological disorder such as Raynaud's syndrome, movement impairment, Parkinson's disease, Huntington's chorea or Alzheimer's disease; immune, cardiovascular, reproductive and endocrine disorders, endotoxin-induced or cirrhotic hypotension, septic shock, diseases related to the respiratory and gastrointestinal systems such as decreased intestinal motility such as Paralytic ileus caused by peritonitis, surgery, or other noxious situations, extended abuse, addiction and relapse indications such as tobacco smoking, heroin addiction, relapse to cocaine-seeking, or alcoholism.

17. The method according to claim 16 wherein the condition associated with the CB-1 receptor is obesity.

18. A compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein:

Y is phenyl, a 5- or 6-membered heteroaryl group, or a 9-membered bicyclic heteroaryl group attached to the urea through the 5-membered ring;

W is $COOR^1$, COR^1, C_{1-6}alkoxy, C_{1-3}fluoroalkoxy, C_{1-3}alkoxyC_{1-3}alkoxy, $-(CH_2)_m-NR^2R^3$, $-O(CH_2)_n-NR^2R^3$, C_{1-6}alkylthio, fluoro, chloro or 5- or 6-membered heteroaryl optionally substituted by C_{1-3}alkyl;

W^1 is hydrogen, halogen or C_{1-3}alkoxy;

Z is C_{1-3}alkylene, C_{2-3}alkenylene or a bond;

Q is phenyl, pyridyl or a 9-membered bicyclic heteroaryl group;

T is halogen, $COOR^1$, COR^1, C_{1-6}alkyl, C_{1-6}alkylthio, $-(CH_2)_m-NR^2R^3$, or a 5- to 10-membered heteroaryl group optionally substituted by C_{1-3}alkyl; or when Z is C_{1-3}alkylene or C_{2-3}alkenylene, then T may be hydrogen;

T^1 and T^2 are independently selected from hydrogen, halogen and hydroxy;

R^1 is C_{1-6}alkyl or phenyl or a 5- or 6-membered heteroaryl or heterocyclyl group;

R^2 and R^3 together with the nitrogen to which they are attached form a 5- to 7-membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and NR^4, and optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy;

m is 0, 1, 2 or 3; and

n is 2 or 3;

provided that the compound is not:

1-Benzo[b]thiophen-2-yl-3-(2-methylphenyl)urea,
4-[3-(2-Chlorophenyl)ureido]benzoic acid ethyl ester,
4-[3-(4-Methylsulfanylphenyl)ureido]benzoic acid ethyl ester,
4-[3-(4-Chlorophenyl)ureido]benzoic acid ethyl ester,
1-(3-Chlorophenyl)-3-(4-ethoxyphenyl)urea,
4-[3-(3-Chlorophenyl)ureido]benzoic acid ethyl ester,
1,3-Bis(4-acetylphenyl)urea,
4-[3-(4-Fluorophenyl)ureido]benzoic acid ethyl ester,
1-(4-Fluorophenyl)-3-(4-methoxyphenyl)urea,
1-(4-Acetylphenyl)-3-(3-chlorophenyl)urea,
1-(4-Acetylphenyl)-3-(4-chlorophenyl)urea,
1-(4-Chlorophenyl)-3-(4-ethoxyphenyl)urea,
1-(4-Acetylphenyl)-3-(4-fluorophenyl)urea,
4-[3-(4-Fluorophenyl)ureido]benzoic acid methyl ester,
4-[3-(3-Fluorophenyl)ureido]benzoic acid ethyl ester,
4-[3-(2-Fluorophenyl)ureido]benzoic acid ethyl ester,
1-(3-Ethoxyphenyl)-3-(4-fluorophenyl)urea,
1-(4-Chlorophenyl)-3-(4-trifluoromethoxyphenyl)urea,
1-(3-Acetylphenyl)-3-[2-(4-chlorophenyl)ethyl]urea, or
1-(4-Chlorophenyl)-3-[4-(morpholine-4-carbonyl)phenyl]urea.

19. A compound according to claim 18 wherein when Y is phenyl.

20. A compound according to claim 18 wherein when Y is a 5- or 6-membered heteroaryl group it is thienyl, thiazolyl or thiadiazolyl.

21. A compound according to claim 18 wherein when Y is a 9-membered bicyclic heteroaryl group it is benzothienyl or benzothiazolyl.

22. A compound according to claim 19 wherein W is $COOR^1$, COR^1, C_{1-6}alkoxy, C_{1-6}alkylthio, fluoro, chloro, C_{1-3}alkoxyC_{1-3}alkoxy, $-(CH_2)_m-NR^2R^3$, $-O(CH_2)_n-NR^2R^3$, or 5- or 6-membered heteroaryl optionally substituted by C_{1-3}alkyl.

23. A compound according to any one of claims 18 to 22 wherein W^1 is hydrogen.

24. A compound according to any one of claims 18 to 23 wherein Z is C_2alkylene, C_2alkenylene or a bond.

25. A compound according to claim 24 wherein Z is a bond.

26. A compound according to any one of claims 18 to 25 wherein Q is phenyl.

27. A compound according to any one of claims 18 to 26 wherein T is halogen, $COOR^1$, COR^1, C_{1-6}alkyl, $-(CH_2)_m-NR^2R^3$ optionally substituted by 1 or 2 groups independently selected from C_{1-3}alkyl, fluoro and hydroxy, or a 5- to 10-membered heteroaryl group optionally substituted by C_{1-3}alkyl.

28. A compound according to claim 27 wherein when T is $-(CH_2)_m-NR^2R^3$, m is 0 and R^2 and R^3 together with the nitrogen to which they are attached form a 5- to 7-membered heterocyclic ring.

29. A compound according to any one of claims 18 to 28 wherein T^1 and T^2 are hydrogen, halogen or hydroxy.

30. A compound according to claim 29 wherein T^2 is hydrogen.

31. A compound according to any one of claims 18 to 30 wherein the substituents on the groups Y and Q are in the meta and/or para positions relative to the urea.

32. A compound selected from:
2-[3-(4-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
2-[3-(3-Fluorophenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]-4-methylthiazole-5-carboxylic acid ethyl ester
4-Methyl-2-[3-(4-methylsulfanylphenyl)ureido]thiazole-5-carboxylic acid ethyl ester
1-(4-Acetylphenyl)-3-benzo[b]thiophen-2-ylurea
1-Benzo[b]thiophen-2-yl-3-(4-methanesulfonylphenyl)urea
4-[3-(4-Fluoro-2-methylphenyl)ureido]benzoic acid ethyl ester
4-[3-(2,4,6-Trifluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(2,4-Difluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(3,4-Difluorophenyl)ureido]benzoic acid ethyl ester

4-[3-(2-Chloro-4-fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluoro-3-methylphenyl)ureido]benzoic acid ethyl ester
4-[3-(3-Chloro-4-fluorophenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Fluoro-3-methoxyphenyl)ureido]benzoic acid ethyl ester
1-(4-Ethoxyphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluorophenyl)ureido]-3-methylbenzoic acid methyl ester
4-[3-(4-Fluorophenyl)ureido]-3-hydroxybenzoic acid methyl ester
1-(2-Thiophen-2-ylethyl)-3-(4-methylphenyl)urea
1-(4-Methoxyphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethoxyphenyl)urea
1-(4-Difluoromethoxyphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(2-Thiophen-2-ylethyl)-3-(4-trifluoromethylphenyl)urea
1-(3-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Butylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Acetylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(3-Ethylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Fluorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Chlorophenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Methylsulfanylphenyl)-3-(2-thiophen-2-ylethyl)urea
1-(4-Isopropylphenyl)-3-(2-thiophen-2-ylethyl)urea
4-(3-Benzothiazol-6-ylureido)benzoic acid ethyl ester
4-[3-(4-Imidazol-1-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(6-Fluorobenzothiazol-2-yl)ureido]benzoic acid ethyl ester
5-[3-(4-Ethoxycarbonylphenyl)ureido]furan-2-carboxylic acid methyl ester
4-[3-(1H-Indol-6-yl)ureido]benzoic acid ethyl ester
4-[3-(3-Methoxycarbonylphenyl)ureido]benzoic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]thiophene-3-carboxylic acid methyl ester
4-{3-[2-(1-Methyl-1H-pyrrol-2-yl)ethyl]ureido}benzoic acid ethyl ester
4-[3-(6-Methoxypyridin-3-yl)ureido]benzoic acid ethyl ester
6-[3-(4-Ethoxycarbonylphenyl)ureido]nicotinic acid methyl ester
4-[3-(6-Chloropyridin-3-yl)ureido]benzoic acid ethyl ester
4-[3-(4-Carboxymethylphenyl)ureido]benzoic acid ethyl ester
4-[3-(1H-Indol-5-yl)ureido]benzoic acid ethyl ester
1-(4-Fluorophenyl)-3-(4-morpholin-4-ylphenyl)urea
1-Benzothiazol-6-yl-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(4-imidazol-1-ylphenyl)urea
6-[3-(4-Fluorophenyl)ureido]nicotinic acid methyl ester
1-(6-Chlorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(6-Fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(4,6-Difluorobenzothiazol-2-yl)-3-(4-fluorophenyl)urea
1-(4-Fluorophenyl)-3-(6-methoxybenzothiazol-2-yl)urea

1-(4-Fluorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl]urea
3-[3-(4-Fluorophenyl)ureido]benzoic acid methyl ester
1-(4-Fluorophenyl)-3-(2-fluorophenyl)urea
3-[3-(4-Fluorophenyl)ureido]benzoic acid ethyl ester
1-(4-Fluoro-3-methylphenyl)-3-(4-fluorophenyl)urea
4-{3-[3-(2-Methylpyrimidin-4-yl)phenyl]ureido}benzoic acid ethyl ester
4-[3-(1-Oxoindan-5-yl)ureido]benzoic acid ethyl ester
4-[3-(6-Morpholin-4-ylpyridin-3-yl)ureido]benzoic acid ethyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]thiazole-5-carboxylic acid methyl ester
4-[3-(3-Ethoxycarbonylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid propyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid pentyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid isobutyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid phenyl ester
4-{3-[4-(1,1,2,2-Tetrafluoroethoxy)phenyl]ureido}benzoic acid ethyl ester
4-[3-(3-Oxazol-5-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylmethylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-[1,2,3]Thiadiazol-4-ylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Propionylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Acetylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Benzoylphenyl)ureido]benzoic acid ethyl ester
4-{3-[4-(4,5-Dihydrooxazol-2-yl)phenyl]ureido}benzoic acid ethyl ester
4-{3-[4-(2-Methylpyrimidin-4-yl)phenyl]ureido}benzoic acid ethyl ester
1-(4-Fluorophenyl)-3-(4-pyrrol-1-ylphenyl)urea
1-(4-Fluorophenyl)-3-(2-methylbenzothiazol-5-yl)urea
1-(4-Fluorophenyl)-3-(3-oxazol-5-ylphenyl)urea
1-(4-Fluorophenyl)-3-(4-propionylphenyl)urea
1-(4-Fluorophenyl)-3-[4-(2-methylpyrimidin-4-yl)phenyl]urea
4-[3-(4-Ethoxycarbonylphenyl)ureido]benzoic acid butyl ester
2-[3-(4-Ethoxycarbonylphenyl)ureido]-4-methylpyrimidine-5-carboxylic acid ethyl ester
4-[3-(4-Oxazol-5-yl phenyl)ureido]benzoic acid ethyl ester
2-Chloro-4-[3-(4-ethoxycarbonylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]-2-methoxybenzoic acid ethyl ester
4-[3-(4-Ethoxycarbonylphenyl)ureido]-3-methoxybenzoic acid ethyl ester
6-[3-(4-Ethoxycarbonylphenyl)ureido]nicotinic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]-3-hydroxy benzoic acid ethyl ester
4-[3-(3-Acetylphenyl)ureido]benzoic acid ethyl ester
4-[3-(4-Butyrylphenyl)ureido]benzoic acid ethyl ester
4-{3-[4-(1H-Pyrazol-3-yl)phenyl]ureido}benzoic acid ethyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid propyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid pentyl ester
4-[3-(4-Fluorophenyl)ureido]benzoic acid isobutyl ester

4-[3-(4-Fluorophenyl)ureido]benzoic acid phenyl ester
{4-[3-(4-Fluorophenyl)ureido]phenyl}acetic acid ethyl ester
1-(4-Benzoylphenyl)-3-(4-fluorophenyl)urea
1-(4-Butyrylphenyl)-3-(4-fluorophenyl)urea
4-[3-(4-Fluorophenyl)ureido]benzoic acid butyl ester
2-Chloro-4-[3-(4-fluorophenyl)ureido]benzoic acid ethyl ester
1-[2-(3-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea
1-[2-(2-Fluorophenyl)ethyl]-3-(4-isopropylphenyl)urea
1-[2-(3-Fluorophenyl)ethyl]-3-(4-trifluoromethylphenyl)urea
1-(4-Isopropylphenyl)-3-thiazol-2-ylurea
1-(4-Acetylphenyl)-3-(4-bromophenyl)urea
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(3-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(4-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl] urea
1-(3,4-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(6-pyrrolidin-1-ylpyridin-2-yl)phenyl] urea
1-(4-Azepan-1-yl-3-fluorophenyl)-3-(4-chlorophenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-pyrrolidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethoxy)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-methoxyethoxy)phenyl] urea
1-(4-Chlorophenyl)-3-[3-(2-isopropylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-[1,4]oxazepan-4-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-pyrrol-1-ylphenyl) urea
4-[3-(3-Fluoro-4-piperidin-1-ylphenyl)ureido]benzoic acid ethyl ester
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methoxyethoxy)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-morpholin-4-ylethoxy)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyridin-3-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(6-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-hydroxypiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyridin-2-yl-phenyl) urea
1-(4-Chlorophenyl)-3-(4-pyridin-4-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(2-piperidin-1-ylpyrimidin-4-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[4-(2-morpholin-4-ylethyl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(2,3-Dihydrobenzofuran-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3,5-Dimethoxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(3-pyrazol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)phenyl] urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrrol-1-ylphenyl) urea

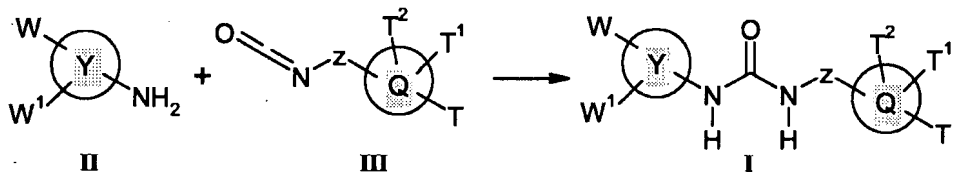
1-(4-Morpholin-4-ylmethylphenyl)-3-(3-pyrrol-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[4-(4,4-difluoropiperidin-1-yl)-3-fluorophenyl] urea
1-(4-Butyrylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(1-Methyl-1H-indazol-5-yl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Morpholin-4-ylmethylphenyl)-3-(4-pyrazol-1-ylphenyl) urea
1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3,5-Dichlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Chloro-4-fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Ethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-[3-(2-methyl-2H-pyrazol-3-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(3-methylpiperidin-1-yl)phenyl] urea
1-Benzo[1,3]dioxol-5-yl-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(2-methylpiperidin-1-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-methoxyphenyl) urea
1-(4-Chloro-2-hydroxyphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-[3-(2-methylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-trifluoromethylpiperidin-1-yl)phenyl] urea
1-(4-Chlorophenyl)-3-[3-fluoro-4-(4-methylpiperidin-1-yl)phenyl] urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-phenoxyphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-phenoxyphenyl) urea
1-(4-Fluorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(3-methoxyphenyl) urea
1-(4-Cyanophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chloro-3-trifluoromethylphenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Fluoro-4-piperidin-1-ylphenyl)-3-(4-trifluoromethylphenyl) urea
1-(3-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(4-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Chlorophenyl)-3-(3-dimethylaminophenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-morpholin-4-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-(3-pyrrol-1-ylphenyl) urea
1-(3,5-Dichlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(3-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(3,5-Bis-trifluoromethylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea
1-(4-Acetylphenyl)-3-[4-(morpholine-4-carbonyl)phenyl] urea
1-(4-Acetylphenyl)-3-[3-(6-methoxypyridin-2-yl)phenyl] urea
1-(4-Acetylphenyl)-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chlorophenyl)-3-(3-fluoro-4-piperidin-1-ylphenyl) urea
1-(3-Chloro-4-morpholin-4-ylphenyl)-3-(4-chlorophenyl) urea
1-(4-Chlorophenyl)-3-(4-piperidin-1-ylphenyl) urea
1-(4-Acetylphenyl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl) urea

1-(4-Butyrylphenyl)-3-(4-piperidin-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-(4-morpholin-4-ylmethylphenyl) urea
1-(4-Chlorophenyl)-3-(1-methyl-1H-indazol-5-yl) urea
1-(4-Chlorophenyl)-3-[3-(2-pyrrolidin-1-ylpyrimidin-4-yl)phenyl] urea
1-(4-Chlorophenyl)-3-(4-pyrazol-1-ylphenyl) urea
1-[2-(4-Chlorophenyl)ethyl]-3-[4-(morpholine-4-carbonyl)phenyl] urea
and pharmaceutically acceptable salts thereof.

33. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 18 to 32, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

34. A process for the production of a compound of formula (I) as defined in any one of claims 18 to 32 which comprises:

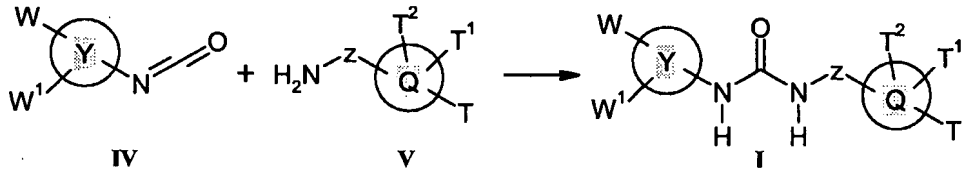
a) combining an amine of formula (II) with an isocyanate of formula (III) in a suitable solvent:



II III I

or

b) combining an amine of formula (IV) with an isocyanate of formula (V) in a suitable solvent:



IV V I

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
21 December 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ARYL UREA DERIVATIVES FOR TREATING OBESITY

(57) Abstract: A method of treating a condition associated with the CB-1 receptor, in particular obesity, by administering an effective amount of an aryl urea CB-1 receptor modulating compound to a subject in need of such treatment.

WO 2006/018662 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/050131

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/426 A61K31/381 A61K31/428 A61K31/341 A61K31/404
A61K31/44 A61K31/455 A61P25/18 A61P25/08 A61P3/04
A61P25/16 A61P25/28 A61P25/32 A61P25/34 A61P25/36
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/048319 A (7TM PHARMA A/S; HOEGBERG, THOMAS; BJURLING, ANNA, EMELIE; RECEVEUR, JE) 10 June 2004 (2004-06-10) examples 9,10,110,111	1,2, 5-19, 22-33
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GWIAZDA, ZYGMUNT: "Infrared spectrophotometric method for determining diuron in industrial products" XP002390022 retrieved from STN Database accession no. 91:84890 abstract & ORGANIKA 76-83 CODEN: ORGAD2; ISSN: 0137-9933, 1978,	18,19, 22,24, 25,27, 29-31

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2006	30. 10. 2006

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/050131

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NG PH BUU-HOI ET AL: "New NN'-disubstituted thioureas and ureas of biological interest" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL SOCIETY. LETCHWORTH, GB, 1958, pages 2815-2821, XP002128092 ISSN: 0368-1769 -----	18,19, 22-27, 29-31,33

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Form PCT/ISA/210 (continuation of second sheet) (April 2005)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 5-18, 22-33 (partially); 2, 19 (completely)

   The compounds of claim 18, Y being phenyl, pharmaceutical compositions comprising said compounds and a method of treatment according to claim 1 by administering a compound of Formula I, Y being phenyl

   ---

2. claims: 1, 5-18, 22-33 (partially); 3, 20 (completely)

   The compounds of claim 18, Y being a 5- or 6-membered heteroaryl group, pharmaceutical compositions comprising said compounds and a method of treatment according to claim 1 by administering a compound of Formula I, Y being a 5- or 6-membered heteroaryl group

   ---

3. claims: 1, 5-18, 22-33 (partially); 4, 21 (completely)

   The compounds of claim 18, Y being a 9-membered bicyclic heteroaryl group attached to the urea through the 5-membered ring, pharmaceutical compositions comprising said compounds and a method of treatment according to claim 1 by administering a compound of Formula I, Y being a 9-membered bicyclic heteroaryl group attached to the urea through the 5-membered ring

   ---

4. claim: 34 (completely)

   The process of claim 34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/050131

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1,2,5-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 5-18, 22-33 (partially); 2, 19 (completely)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2005/050131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004048319 A	10-06-2004	AU 2003226929 A1	18-06-2004